United States District Court
EASTERN DISTRICT OF TEXAS
TYLER DIVISION

ALLERGAN, INC.	§	
	§	**Cause No. 6:11-cv-441**
v.	§	**Consolidated Case**
	§	
SANDOZ INC., ET AL.	§	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

Plaintiff Allergan, Inc. filed this consolidated action under the Hatch-Waxman Act alleging patent infringement against Defendants Sandoz Inc.; Lupin Pharmaceuticals, Inc. and Lupin Ltd. (collectively Lupin); Hi-Tech Pharmacal Co., Inc.; and Watson Laboratories, Inc., Watson Pharmaceuticals, Inc., and Watson Pharma, Inc. (collectively Watson).

This dispute revolves around Defendants seeking approval to market and sell generic drugs. Allergan alleges that Defendants infringe its patents and that injunctive relief is warranted to prevent Defendants from introducing generic versions of Allergan's drug Lumigan® 0.01% bimatoprost ophthalmic solution. Defendants deny infringement and contend that the patents are invalid and unenforceable.

The Court conducted a bench trial from July 15–19, 2013. Having considered the parties' stipulations, the pleadings, the testimony and credibility of the witnesses, the evidence, the arguments and briefs of counsel, and the applicable law—including the parties' supplemental briefing on the latest Federal Circuit decision that issued after the bench trial (*see* Doc. No. 301)—the Court enters the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

I. BACKGROUND

This is a patent infringement action filed under the Hatch-Waxman Act. Congress passed the Hatch-Waxman Act in 1984 to promote the manufacturing of generic pharmaceuticals. *See* Drug Price Competition and Patent Term Restoration Act, 98 Stat. 1585 (1984); *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2574 (2011). "Under this law, 'generic drugs' can gain [Federal Drug Administration (FDA)] approval simply by showing equivalence to a reference listed drug that has already been approved by the FDA." *Mensing*, 131 S. Ct. at 2574. "This allows manufacturers to develop generic drugs inexpensively, without duplicating the clinical trials already performed on the equivalent brand-name drug." *Id*.

Allergan obtained FDA approval for Lumigan® 0.03% bimatoprost ophthalmic solution in 2001. In late 2010, Allergan obtained FDA approval for Lumigan® 0.01% bimatoprost ophthalmic solution for the reduction of elevated intraocular pressure in certain patients, including those with open angle glaucoma or ocular hypertension. The active ingredient in Lumigan® is the prostaglandin analog bimatoprost, which operates by increasing the outflow of aqueous humor from the eye.

Defendants have each filed an Abbreviated New Drug Application (ANDA) for FDA approval to market and sell a generic version of Plaintiff's Lumigan® 0.01% bimatoprost ophthalmic solution. Defendants seek to market and sell their generic versions prior to the expiration of the patents listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations publication (known as the Orange Book) as covering Allergan's Lumigan® 0.01% bimatoprost ophthalmic solution.

Defendants filed their ANDAs pursuant to a procedure called paragraph IV certification. *See* 21 U.S.C. § 355(j)(2)(A). Under this procedure, Defendants certified that the patents listed in the Orange Book are invalid or will not be infringed by their generic pharmaceuticals. "Such a

certification constitutes an artificial act of infringement." *Pozen Inc. v. PAR Pharm., Inc.*, 696 F.3d 1151, 1157 (Fed. Cir. 2012). Accordingly, Allergan filed complaints against Defendants for infringement of its five patents covering the 0.01% bimatoprost solution: U.S. Patent Nos. 7,851,504 (the '504 Patent); 8,278,353 (the '353 Patent); 8,299,118 (the '118 Patent); 8,309,605 (the '605 Patent); and 8,339,479 (the '479 Patent). In light of Defendants' alleged infringement, Allergan also seeks injunctive relief to prevent Defendants from marketing and selling generic versions of Allergan's drug until the expiration of the patents. Generally, Defendants deny infringing the patents and maintain that they are invalid, primarily based upon obviousness.

At the time of the bench trial in this case, the parties raised several legal and factual issues for resolution: first, whether Defendants' proposed generic drugs infringe Allergan's patents; second, whether Allergan's patents are invalid and unenforceable; and third, whether injunctive relief is justified.

The Court reaches the following conclusions on these issues:

1) Defendants' proposed generic drug products infringe Allergan's patents.
2) Allergan's patents are not invalid and are enforceable.
3) Allergan is entitled to a permanent injunction preventing Defendants from introducing generic versions of Lumigan® 0.01% until the expiration of Allergan's patents.

These issues are more fully addressed in the findings of fact and conclusions of law set forth below.[1] The findings are limited to the relevant factual disputes raised.[2]

[1] Any finding of fact more properly characterized as a conclusion of law is adopted as such. Any conclusion of law more properly characterized as a finding of fact is adopted as such.

[2] For purposes of this order, the Court only considered relevant and admissible evidence.

II. FINDINGS OF FACT

1. The facts set forth in the background section—whether disputed or undisputed—are found by the Court to be true by a preponderance of the evidence.

A. The Parties' Stipulations

Prior to the commencement of trial, the parties stipulated that certain facts are true (Doc. No. 207 at 24–27). The Court considers these facts as conclusively established.

2. Subject matter jurisdiction is proper in this Court for claims asserted by Allergan under 35 U.S.C. § 271(e)(2)(A), and for Defendants' declaratory judgment counterclaims.
3. The parties do not contest personal jurisdiction or venue in this Court solely for the limited purpose of this action only.
4. Allergan, Inc. is a Delaware corporation with its principal place of business at 2525 Dupont Drive, Irvine, California 92612.
5. Sandoz, Inc. is a Colorado corporation with its principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540.
6. Lupin Ltd. is a company organized and existing under the laws of India, with a place of business at Laxmi Towers "B" Wing, 5th floor, Banda Kurla Complex, Mumbai 400 051, India.
7. Lupin Pharmaceuticals, Inc. is a Virginia corporation with a place of business at Harborplace Tower, 111 South Calvert Street, Baltimore, Maryland 21202. Lupin Pharmaceuticals, Inc. is a wholly owned subsidiary of Lupin Ltd.
8. Hi-Tech Pharmacal Co., Inc. is a corporation incorporated under the laws of the State of Delaware, with a place of business at 369 Bayview Avenue, Amityville, NY 11701.

9. Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.) is a Nevada corporation with a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054.
10. Watson Laboratories, Inc. is a Nevada corporation with a place of business at 311 Bonnie Circle, Corona, California 92880. Watson Laboratories, Inc. is a wholly owned subsidiary of Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.).
11. Watson Pharma, Inc. is a Delaware corporation having a place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054. Watson Pharma, Inc. is a wholly owned subsidiary of Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.).
12. The ’504 Patent issued on December 14, 2010, and is entitled “Enhanced Bimatoprost Ophthalmic Solution.” The application for the ’504 Patent was filed on March 16, 2005.
13. The ’353 Patent issued on October 2, 2012, and is entitled “Enhanced Bimatoprost Ophthalmic Solution.” The application for the ’353 Patent was filed on February 10, 2012, and is a continuation of the application that led to the ’504 Patent.
14. The ’118 Patent issued on October 30, 2012, and is entitled “Enhanced Bimatoprost Ophthalmic Solution.” The application for the ’118 Patent was filed on February 10, 2012, and is a continuation of the application that led to the ’504 Patent.
15. The ’605 Patent issued on November 13, 2012, and is entitled “Enhanced Bimatoprost Ophthalmic Solution.” The application for the ’605 Patent was filed on December 10, 2010, and is a continuation of the application that led to the ’504 Patent.

16. The ’479 Patent issued on December 25, 2012, and is entitled “Enhanced Bimatoprost Ophthalmic Solution.” The application for the ’479 Patent was filed on January 9, 2009, and is a continuation of the application that led to the ’504 Patent.
17. The following claim of the ’504 Patent is asserted in this case: 2.
18. The following claims of the ’353 Patent are asserted in this case: 1, 7, 8, 15, and 16.
19. The following claims of the ’118 Patent are asserted in this case: 1, 7, 8, 15, and 16.
20. The following claims of the ’605 Patent are asserted in this case: 1, 6, 10, and 12.
21. The following claims of the ’479 Patent are asserted in this case: 2, 6, 11, 13, 15, and 16.
22. The named inventors of the patents in Suit are Chin-Ming Chang, James N. Chang, Rhett M. Schiffman, R. Scott Jordan, and Joan-En Chang-Lin.
23. Sandoz filed ANDA No. 203506 with the FDA seeking to market its bimatoprost ophthalmic solution, 0.01% product.
24. The formulation of Sandoz’s proposed generic bimatoprost ophthalmic solution, 0.01% product is set forth in Sandoz’s ANDA.
25. Lupin filed ANDA No. 202911 with the FDA seeking to market its bimatoprost ophthalmic solution, 0.01% product.
26. The formulation of Lupin’s proposed generic bimatoprost ophthalmic solution, 0.01% product is set forth in Lupin’s ANDA.
27. Hi-Tech filed ANDA No. 203604 with the FDA seeking to market its bimatoprost ophthalmic solution, 0.01% product.
28. The formulation of Hi-Tech’s proposed generic bimatoprost ophthalmic solution, 0.01% product is set forth in Hi-Tech’s ANDA.

29. The pH stability specification set forth in ANDA No. 203604 for Hi-Tech's proposed bimatoprost 0.01% product is 6.8 to 7.2.

30. Watson filed ANDA No. 203748 with the FDA seeking to market its bimatoprost ophthalmic solution, 0.01% product.

31. The formulation of Watson's proposed generic bimatoprost ophthalmic solution, 0.01% product is set forth in Watson's ANDA.

B. Lumigan® 0.03% Bimatoprost Ophthalmic Solution

32. Open-angle glaucoma is a condition that affects millions of patients worldwide.

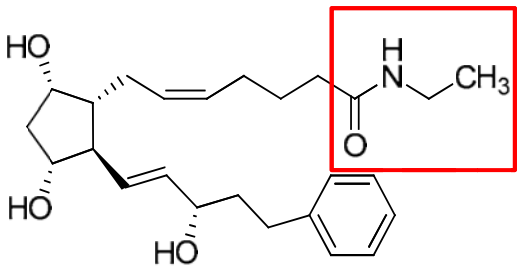
33. One major cause of the condition is elevated intraocular pressure (IOP). Increased ocular pressure is believed to damage and eventually kill optic nerve cells.

34. If left untreated, glaucoma causes gradual vision loss and can ultimately lead to complete blindness.

35. Currently there are no known cures for optic nerve cell damage. But there are surgical and pharmacological treatments that can reduce IOP, therefore slowing or abating the progression of glaucoma in affected patients.

36. Allergan first developed Lumigan® 0.03% to reduce IOP.

37. The active ingredient in Lumigan® 0.03% is bimatoprost. The chemical structure of bimatoprost is as follows:



38. Bimatoprost is structurally related to the naturally occurring prostaglandin molecule $PGF_{2\alpha}$, and is one of several prostaglandin-analog drugs that are used for the treatment of glaucoma.
39. One structural difference from other prostaglandin analogs is the amide group, highlighted in the red box above.
40. In 2001, the FDA approved the use of bimatoprost in Lumigan® 0.03% for treating glaucoma and ocular hypertension.
41. Lumigan® 0.03% includes the preservative benzalkonium chloride (BAK) at a concentration of 50 parts per million (ppm) to inhibit bacterial growth. It also includes citric acid monohydrate, a phosphate buffer, and sodium chloride. The target pH for Lumigan® 0.03% is 7.3.
42. Main competitors to Lumigan® 0.03% included the prostaglandin analogs Xalatan® (with the active ingredient latanoprost) and Travatan® (with the active ingredient travoprost).
43. Although Xalatan® and Travatan® are prostaglandin analogs, they act by different means than Lumigan®. Xalatan® and Travatan® are prodrugs. Prodrugs are administered in an inactive form but are converted upon administration into an active form, in this case the free-acid form. Conversely, bimatoprost is administered in its active form.
44. Clinical studies showed that Lumigan® 0.03% lowered IOP more than other available drugs, including Xalatan®.

45. Although effective at lowering IOP, Lumigan® 0.03% had a severe side effect. The use of Lumigan® 0.03% caused more frequent and severe conjunctival hyperemia—or red eye—than other drugs.

46. Experts for the parties agreed that hyperemia associated with Lumigan® 0.03% was severe enough that it caused glaucoma patients to stop taking the medication without consulting or notifying their physicians.

47. Although hyperemia would cease upon termination of the treatment, the patient's IOP remained unregulated and could therefore result in increased vision loss or blindness.

48. Because vision loss due to glaucoma progresses gradually, a patient does not recognize or appreciate the harm by discontinuing treatment.

C. Development of Lumigan® 0.01% Bimatoprost Ophthalmic Solution

49. In order to address the hyperemia concerns of Lumigan® 0.03%, Allergan began working on a solution in February 2002. Allergan's goal was to maintain the efficacy of Lumigan® 0.03% while reducing the incidence and severity of hyperemia.

50. Allergan believed this was a challenging proposal due to the properties of Lumigan® 0.03%. The active ingredient bimatoprost was effective in lowering IOP, but it also caused the hyperemia side effect.

51. At first, Allergan looked for solutions other than changing the 0.03% concentration of bimatoprost because its researchers believed that decreasing the amount of bimatoprost would result in a decreased efficacy in lowering IOP.

52. Allergan attempted a number of alternative formulations before achieving its desired result. It took Allergan approximately a year and a half of formulation work before uncovering the solution.

53. In one formulation, Allergan used 0.03% bimatoprost with a cyclodextrin. The cyclodextrin would complex with the bimatoprost—or envelop the bimatoprost—and reduce the amount of free (non-complexed) drug available on the ocular surface. Allergan believed that reducing the amount of free drug on the eye would result in less hyperemia. Although this work ultimately led to another patent issued to Robert Lyons and James Chang, it proved unsuccessful in achieving Allergan's goal of reduced hyperemia.

54. Similarly, Allergan probed the efficacy of several other formulations. These included formations contained 0.03% bimatoprost and the following: (1) Refresh Liquigel; (2) high calcium borate buffer; (3) castor oil emulsion; and (4) gellan gum.

55. Many of these formulations increased the viscosity of the drug to attempt the keep the active ingredient on the surface of the eye longer so the drug could slowly penetrate the cornea. Allergan believed that delaying the full release of the drug would curb severe hyperemia. Other approaches, including that for the calcium borate buffer system, were explored in order to cause vasoconstriction. Allergan used this system in an attempt to substitute the citric acid/phosphate buffer system in Lumigan® 0.03%. Hyperemia is caused by vasodilation, or the enlargement of blood vessels. Therefore, Allergan believed increasing vasoconstriction would reduce hyperemia. Unfortunately, none of these formulations satisfied Allergan's criteria of lowering hyperemia.

56. At this same time, Allergan also worked on formulations eliminating BAK as an ingredient. It was understood that BAK—although widely used in ophthalmic therapies—had negative side effects on the eye. Because BAK irritated the eye, Allergan pursued formations eliminating it as an ingredient.

57. In one formulation, Allergan replaced BAK with Purite®. Purite® is a less irritating preservative that Allergan had used in other glaucoma pharmaceuticals. But this formulation failed because bimatoprost was unstable when combined with Purite®.

58. In another attempt, Allergan used nitric oxide scavengers to control vasodilatation. Under this theory, Allergan hypothesized that bimatoprost could be interacting with nitric oxide to cause hyperemia. Therefore, Allergan assumed using the nitric oxide scavengers would reduce the available nitric oxide, and potentially decrease the prevalence of hyperemia.

59. In pursuing this hypothesis, Allergan created two different "cocktail" formulations in June 2003, each containing 0.03% bimatoprost. One cocktail was called the nitric oxide scavenger cocktail and the other the nitric oxide scavenger emulsion cocktail. The water-soluble scavengers were used in the nitric oxide scavenger cocktail while the oil-soluble scavengers were used in the emulsion cocktail.

60. Vitamin E-TPGS is one of the antioxidants included in the emulsion cocktail because of its known properties as an antioxidant and as a surfactant solubilizer.

61. Allergan observed a surprising result during testing of the emulsion cocktail. Although the ultimate goal was hyperemia reduction, Allergan observed no changes or reduction in hyperemia while testing the emulsion cocktail. But Allergan unexpectedly observed that the emulsion cocktail showed a greater IOP-lowering effect.

62. In investigating the cause of the increased IOP lowering, Allergan concluded that the Vitamin E-TPGS—that was included as a solubilizer—also potentially acted as a permeation enhancer.

63. Thus, Allergan found this formulation to be a potential lead for increasing the efficacy of bimatoprost penetration into the eye to increase the IOP lowering effect.

64. In December 2003, Allergan next conducted studies addressing the impact of Vitamin E-TPGS on preservatives. Allergan observed that Vitamin E-TPGS formulations with BAK were not meeting pharmacopeia requirements for antimicrobial preservative effectiveness. In effect, Vitamin E-TPGS reduced the preservative effectiveness of BAK. Allergan observed this same result when Allergan combined Vitamin E-TPGS with the gentler preservative Purite®.

65. In January 2004—two years into Allergan's research—Allergan studied Vitamin E-TPGS formulations focusing on the preservative efficacy of BAK at different concentrations. Allergan sought to study the level of BAK required in the formulation to meet preservative effectiveness requirements. This was the first instance since initiating its research to improve upon Lumigan® 0.03% that Allergan decided to raise the amount of BAK in the formulation. In light of this testing, Allergan still sought to keep the amount of preservative at a minimum.

66. In 2004, Allergan conducted *in vivo* and *in vitro* studies in rabbits to compare the new Vitamin E-TPGS formulations with Lumigan® 0.03%.

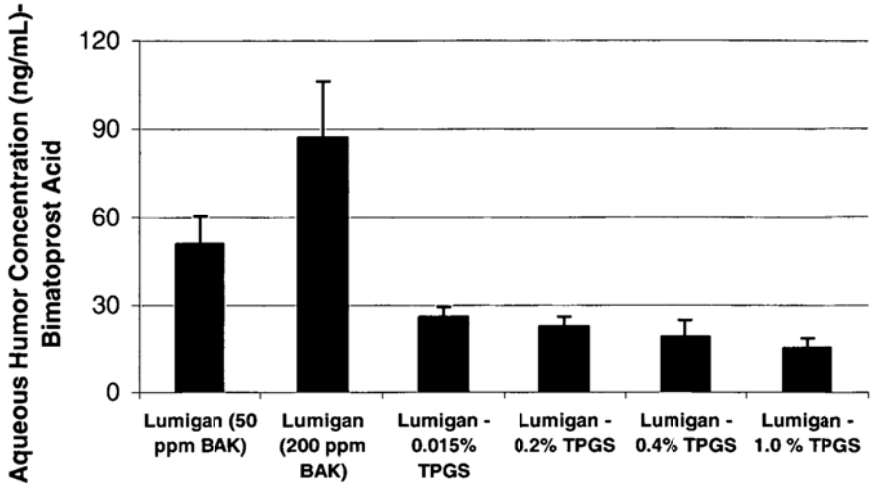
67. In this study, all formulations contained 0.03% bimatoprost. One set of testing included several concentrations of Vitamin E-TPGS with 100 ppm BAK. The control group for this dataset was Lumigan® 0.03% with 50 ppm BAK. Another testing set included various concentrations of Vitamin E-TPGS with 200 ppm BAK. Lumigan® 0.03% with 200 ppm BAK was the control group for this batch. Allergan included the control groups only for comparison purposes regarding the efficacy of the Vitamin E-TPGS formulations.

68. Allergan expected the higher Vitamin E-TPGS formulations to exhibit the greatest amount of corneal penetration.

69. To Allergan's surprise, the control group formulation with 0.03% bimatoprost and 200 ppm BAK—but without any Vitamin E-TPGS—exhibited extraordinary increases in bimatoprost's *in vivo* and *in vitro* corneal penetration.

70. The following figure from Allergan's testing later became a figure in its patents on Lumigan® 0.01% and demonstrates the unexpected results:

Fig. 1



(PTX-1 at 2).

71. After this discovery, Allergan made the bimatoprost formulation with 200 ppm BAK the leading candidate for further investigation.

72. Even though the bimatoprost formulation with 200 ppm BAK showed promise, the scientists at Allergan were not entirely convinced of its potential. For example, in June 2004, inventor Scott Jordan explained that the "lead formulation, believe it or not, is Lumigan® with 200 ppm BAK" (PTX-240). Scientists at Allergan still viewed this

formulation as a last resort because BAK is damaging to the cells on the ocular surface. Allergan understood that at higher concentrations, BAK increased the ocular penetration by compromising the cell layer integrity and increased toxicity. Allergan recognized that BAK was effective as a preservative, but was cautious about its use in higher concentrations.

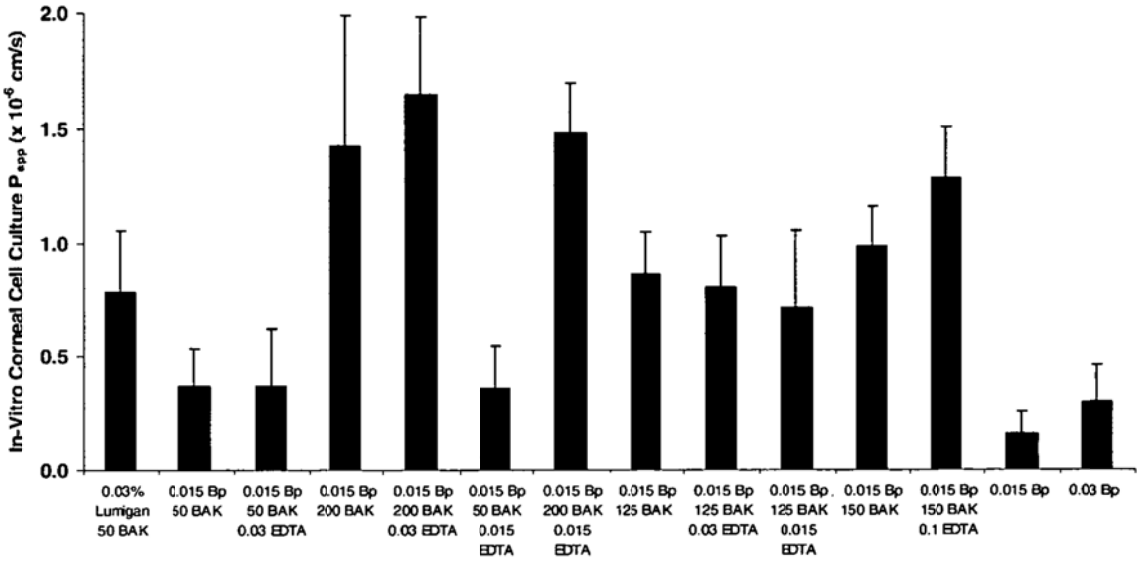
73. Because of the undesired side effects of using BAK, Allergan still pursued other alternatives, including calcium-borate and cyclodextrin formulations.

74. In June 2004, Allergan experimented with formations including increased concentrations of BAK—up to 150 ppm—with the chelating agent EDTA. This was also the first instance in which Allergan studied the effects on formulations of decreasing the concentration of the active ingredient bimatoprost. In this instance, Allergan tested formulations at 0.015% bimatoprost. EDTA has both antioxidant effects and acts as a penetration enhancer. Allergan believed that it could reduce the concentration of BAK because of EDTA's penetration-enhancing properties. Therefore, Allergan surmised that including BAK and EDTA with lower concentrations of bimatoprost could achieve the same IOP lowering efficacy of Lumigan® 0.03%, but reduce instance and severity of hyperemia.

75. The testing confirmed that BAK increased ocular penetration. But the testing established that EDTA had no impact. Accordingly, 0.015% bimatoprost with 200 pm BAK was recommended for further investigation and Phase II human clinical studies.

76. The following figure from Allergan's testing later became a figure in its patents on Lumigan® 0.01% and demonstrates these results:

Fig. 2



(PTX-1 at 3).

77. Allergan's scientists debated whether 0.01% bimatoprost would be worthwhile to include in the Phase II studies. Many of the scientists believed this concentration would be too low to have any efficacy.

78. Although Allergan was moving forward with clinical testing, its scientists remained skeptical that bimatoprost at lower concentrations—including 0.01%—would maintain comparable efficacy to Lumigan® 0.03% and whether the studies would translate in human clinical studies.

79. In November 2004, the testing protocol for Phase II human clinical studies included several formulations, including 0.01% bimatoprost. The clinical hypotheses of the study included that "[a]t least one investigational test formulation has less hyperemia when compared to LUMIGAN® [0.03%] once-daily" and also that "[a]ll investigational test

formulations are comparable to LUMIGAN® [0.03%] once-daily in intraocular pressure lowering effects" (PTX-48 at 13–14).

80. Phase II human clinical testing initiated in January 2005.

81. The inventors filed their patent application in March 2005.

82. In June 2005, the Phase II data showed promising results and were consistent with the inventors' clinical hypotheses.

83. Allergan initiated Phase III studies in late 2005. The results of the study were published in a 2010 peer-reviewed article which concluded that "[b]imatoprost 0.01% was equivalent to bimatoprost 0.03% in lowering IOP throughout 12 months of treatment and demonstrated improved tolerability, including less frequent and severe conjunctival hyperemia" (PTX-135 at 1).

84. In late 2010, the FDA approved Lumigan® 0.01% and Allergan initiated sales of its product.

85. The formulation of Lumigan® 0.01% is:

Table 2.3.P.1-1 List of Components and Quantitative Composition

Component	Concentration (% w/v)	Concentration (mg/mL)	Reference of Quality Standard	Function
Bimatoprost	0.01	0.1	In-house standard	Drug Substance
Benzalkonium Chloride [a]	0.02	0.2	NF/Ph Eur	Preservative
Dibasic Sodium Phosphate Heptahydrate	0.268	2.68	USP	Buffering Agent
Citric Acid Monohydrate	0.014	0.14	USP/Ph Eur	Buffering Agent
Sodium Chloride	0.81	8.1	USP/Ph Eur	Tonicity Agent
Hydrochloric Acid [b]	Adjust pH to 7.3		NF/Ph Eur	pH Adjuster
Sodium Hydroxide [b]			NF/Ph Eur	pH Adjuster
Purified Water [c]	q.s. ad 100	q.s. ad 1 mL	USP/Ph Eur	Vehicle

(PTX-11A at 1).

86. The FDA approved Lumigan® 0.01% "for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension," and it is to be administered using "[o]ne drop in the affected eye(s) once daily in the evening" (PTX-214 at 1).

D. The Asserted Patents

87. The asserted patents all claim priority to the inventors' March 2005 application and share a common specification.

88. After the partied filed their pretrial stipulations of uncontested facts (Section II-A, *supra*) but prior to trial, Allergan further narrowed the asserted claims are as follows:

- '504 Patent: claim 2;
- '353 Patent: claims 1, 7, and 8;
- '118 Patent: claims 1, 7, and 8;
- '605 Patent: claims 1, 6, 10, and 12; and
- '479 Patent: claim 15.

(*See* Doc. No. 265 at 1.)

89. The '504 Patent includes claims to the Lumigan® 0.01% formulation. Asserted claim 2 is reproduced below:

> A composition having a pH of about 7.3 which comprises about 0.01% bimatoprost, about 200 ppm benzalkonium chloride, citric acid monohydrate, a phosphate buffer, and NaCl wherein said composition is an aqueous liquid which is formulated for ophthalmic administration.

(PTX-1 at 6:21–25).

90. Asserted claim 15 of the '479 Patent, which depends from claim 1 of the '479 Patent, is similar and makes explicit that the composition "is for the treatment of elevated intraocular pressure," as shown below:

> 1. A composition for the treatment of elevated intraocular pressure comprising about 0.01% w/v bimatoprost and about 200 ppm benzalkonium chloride, at least one buffer and having a pH of about 7.3 wherein said composition is an aqueous liquid which is formulated for ophthalmic administration.
>
> 15. The composition of claim 1 comprising about 0.01% w/v bimatoprost, about 0.02% w/v benzalkonium chloride, about 0.26% w/v sodium phosphate dibasic heptahydrate, about 0.014% w/v citric acid monohydrate, about 0.8% w/v sodium chloride, and water.

(PTX-5 at 5:47–6:2, 6:40–44).

91. Asserted claims 1, 7, and 8 of the ’353 Patent cover the composition of Lumigan® 0.01% that exhibits the unexpected efficacy and reduced hyperemia observed when compared with Lumigan® 0.03%. Those claims are reproduced below:

> 1. A first composition administered once daily for lowering intraocular pressure in a person with glaucoma or ocular hypertension, the first composition comprising about 0.01% w/v bimatoprost and about 0.02% benzalkonium chloride, wherein the first composition lowers intraocular pressure and results in less hyperemia as compared to the once daily administration of a second composition comprising 0.03% w/v bimatoprost and 0.005% w/v benzalkonium chloride.
>
> 7. A first composition administered once daily for lowering intraocular pressure in a person with glaucoma or ocular hypertension, the first composition comprising about 0.01% w/v bimatoprost and about 0.02% w/v benzalkonium chloride, wherein the first composition lowers intraocular pressure without a substantial reduction in the intraocular pressure lowering benefit provided by the once daily administration of a second composition comprising 0.03% w/v bimatoprost and 0.005% w/v benzalkonium chloride.
>
> 8. The composition of claim 7 wherein the once daily administration of the first composition results in less hyperemia as compared to the once daily administration of the second composition.

(PTX-2 at 5:48–6:15).

92. Asserted claims 1, 6, 10, and 12 of the ’605 Patent cover a method of using Lumigan® 0.01%, and are reproduced below:

> 1. A method of lowering elevated intraocular pressure in a patient with open-angle glaucoma or ocular hypertension which comprises applying to the eyes of the patient an aqueous solution comprised of:
>
> about 0.01% bimatoprost;
> about 200 ppm benzalkonium chloride;
> the solution having a pH of about 7.3;
> a phosphate buffer; and,
> water.
>
> 6. A method of lowering intraocular pressure in a patient suffering from elevated intraocular pressure which comprises applying to the eyes of the patient an aqueous solution comprising:
>
> 0.01% w/v bimatoprost;
> about 200 ppm benzalkonium chloride;
> the solution having a pH of about 7.3;
> a citric acid buffer; and,
> water.
>
> 7. The method of claim 6 wherein the method is applied to patients suffering from glaucoma.
>
> 10. The method of claim 7 wherein the glaucoma is open angle glaucoma.
>
> 12. A method of treating glaucoma in a patient comprising the following steps:
>
> applying at least once a day a formulation comprising:
> about 0.01% w/v bimatoprost;
> benzalkonium chloride in the amount of 200 ppm;
> at least one buffering agent selected from the group consisting of dibasic sodium phosphate heptahydrate, citric acid monohydrate and EDTA;
> and wherein the formulation has a pH of about 7.3.

(PTX-4 at 5:47–6:30).

93. The ’118 Patent includes claims to a method of using Lumigan® 0.01% that recite the unexpected efficacy and reduced hyperemia observed when compared with Lumigan® 0.03%. Asserted claims 1, 7, and 8 of the ’118 Patent are reproduced below:

> 1. A method of lowering intraocular pressure in a person with glaucoma or ocular hypertension, the method comprising administering once daily to an eye of the person a first composition comprising about 0.01% w/v bimatoprost and about 0.02% benzalkonium chloride, wherein the method lowers intraocular pressure and results in less hyperemia as compared to the once daily administration of a second composition comprising 0.03% w/v bimatoprost and 0.005% w/v benzalkonium chloride.
>
> 7. A method of lowering intraocular pressure in a person with glaucoma or ocular hypertension, the method comprising administering once daily to an eye of the person a first composition comprising about 0.01% w/v bimatoprost and about 0.02% w/v benzalkonium chloride, wherein the method lowers intraocular pressure without a substantial reduction in the intraocular pressure lowering benefit provided by the once daily administration of a second composition comprising 0.03% w/v bimatoprost and 0.005% w/v benzalkonium chloride.
>
> 8. The method of claim 7 wherein the once daily administration of the first composition results in less hyperemia as compared to the once daily administration of the second composition.

(PTX-3 at 5:48–6:16).

94. The Court entered two claim construction orders in this case construing certain terms and rejecting Defendants' indefiniteness claims (Doc. Nos. 118, 173). The Court adopts those constructions for purposes of this order.

i. Allergan's Patents Cover Lumigan® 0.01%

95. The asserted claims cover the formulation for and use of Lumigan® 0.01%. Accordingly, the patents cover the composition of Allergan's branded Lumigan® 0.01% product.

96. Moreover, Lumigan® 0.01% satisfies the clinical performance limitations of the '353 and '118 Patents. For example, claim 7 of the '118 and '353 Patents requires a 0.01% bimatoprost/200 ppm BAK solution that "lowers intraocular pressure without a substantial reduction in the intraocular pressure lowering benefit provided by the once daily administration" of a 0.03% bimatoprost/50 ppm BAK solution. The Court construed

the term "without a substantial reduction in the intraocular pressure lowering benefit" to mean "with nearly equivalent intraocular pressure lowering benefit" (Doc. No. 173 at 15). The Lumigan® 0.01% label states that its IOP-lowering effect is within 0.5 mm Hg of Lumigan® 0.03%, which Allergan's expert explained shows that the two products are nearly equivalent. Furthermore, the clinical trials show that Lumigan® 0.03% and 0.01% had equivalent efficacy in IOP-lowering benefits. Additionally, the Katz paper concluded that Lumigan® 0.01% was "equivalent" to Lumigan® 0.03% "in lowering IOP throughout 12 months of treatment" (PTX-135 at 1). Therefore, the composition and use of Lumigan® 0.01% meet this requirement.

97. Claim 1 of both the '118 and '353 Patents requires a 0.01% bimatoprost/200 ppm BAK solution that "lowers intraocular pressure" when administered once-daily (PTX-3 at 5:48–56; PTX-2 at 5:48–56.) The composition and use of Lumigan® 0.01% satisfy this requirement based on the clinical data discussed above.

98. Claims 1 and 8 of the '118 and '353 Patents further require a 0.01% bimatoprost/200 ppm BAK solution that "results in less hyperemia as compared to the once daily administration" of a 0.03% bimatoprost/50 ppm BAK solution (PTX-3 at 5:53–54, 6:13–14; PTX-2 at 5:53–54, 6:14–15). The Court has construed "results in less hyperemia" to mean "results in hyperemia in fewer patients or the level of hyperemia observed is lower in some patients (or both)" (Doc. No. 173 at 15). Lumigan® 0.01% meets this requirement. For example, Katz reported that Lumigan® 0.01% has "less frequent and severe conjunctival hyperemia" than Lumigan® 0.03% (PTX-135 at 1).

E. Defendants' Proposed Generic Pharmaceuticals

99. Sandoz, Lupin, Watson, and Hi-Tech each filed ANDA applications with the FDA seeking approval to market and sell a generic 0.01% bimatoprost ophthalmic solution.

i. Sandoz's ANDA Filing

100. Sandoz submitted ANDA 203056 to the FDA seeking approval to market and sell a 0.01% bimatoprost ophthalmic solution. The proposed prescribing information for Sandoz's product states that—like Lumigan® 0.01%—it is "for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension" and is to be administered with "one drop in the affected eye(s) once daily in the evening" (PTX-348 at 3).

101. Sandoz's ANDA further states that its product is only "0.5 mm Hg less effective" than a 0.03% bimatoprost product (PTX-348 at 9).

102. The composition of Sandoz's proposed product is set out in the portion of its ANDA reproduced below, which compares the Sandoz product to Lumigan® 0.01%:

Ingredient	Lumigan®(Bimatoprost Ophthalmic Solution, 0.01% (Allergan) Quantity (%)	Bimatoprost Ophthalmic Solution, 0.01% (Sandoz Canada) Quantity (%)
Bimatoprost	0.01	0.01
Benzalkonium chloride[1]	0.02	0.02
Sodium Phosphate Dibasic Heptahydrate[2]	0.268	0.268
Sodium chloride[2]	0.81	0.81
Citric acid, monohydrate[2]	0.014	0.014
Hydrochloric acid	pH adjustment	pH adjustment
Sodium hydroxide	pH adjustment	pH adjustment
Water for injection	q.s to 100 %	q.s 1 mL

(PTX-14C at 31).

103. As the table shows, Sandoz's product contains the same ingredients in the same quantities as claimed in the patents and as compared to Allergan's Lumigan® 0.01%.

104. Regarding the pH of Sandoz's product during its shelf life, Sandoz's ANDA indicates that it will have a pH in the range of 6.8–7.8. Testing on Sandoz's actual proposed product indicates a pH of 7.2.

105. Sandoz has also repeatedly indicated that its proposed product will have the same efficacy and hyperemia profile as Lumigan® 0.01%. For example, Sandoz asked the FDA to grant a waiver from conducting human trials on its product, stating that the product "[c]ontains the same active and inactive ingredients in the same concentration" as Lumigan® 0.01% and that "*in vivo* bioavailability or bioequivalence may be considered self-evident" between its proposed product and Lumigan® 0.01% (PTX-14B at 2). Sandoz's project manager Amanda Skoumbourdis confirmed that Sandoz expects its product will have the same clinical efficacy, side-effect profile, and therapeutic effect as Lumigan® 0.01%.

ii. Lupin's ANDA Filing

106. Lupin submitted ANDA 202911 to the FDA seeking approval to market and sell a 0.01% bimatoprost ophthalmic solution. The proposed prescribing information for Lupin's product states that—like Lumigan® 0.01%—it is "for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension" and is to be administered with "[o]ne drop in the affected eye(s) once daily in the evening." (PTX-13B at 2).

107. Lupin's label states that its product is only "0.5 mm Hg less effective" than a 0.03% bimatoprost product (PTX-13B at 6).

108. The composition of Lupin's proposed product is disclosed in its ANDA in the portion set forth below:

Ingredients	0.01% (0.1 mg/mL)		Category	Reference to Standards	IIG Limits (%)
	Quantity mg/mL	% w/v			
ACTIVE INGREDIENT					
Bimatoprost*	0.100	0.010	Active	IH	--
OTHER INGREDIENTS					
Benzalkonium Chloride Solution 50% eq. to Benzalkonium Chloride**	0.400 0.200	0.040 0.020	Preservative	NF	2.00
Sodium Chloride EMPROVE® Low Endotoxin	8.100	0.810	Tonicity Agent	USP	55.00
Di-sodium Hydrogen Phosphate Heptahydrate (EMPROVE® DAC)	2.680	0.268	Buffering Agent	USP	2.50
Citric Acid Monohydrate (EMPROVE®)	0.140	0.014	Buffering Agent	USP	0.05
Sodium Hydroxide[5]	Q. S.	--	pH Modifier	NF	0.10
Hydrochloric Acid[5]	Q. S.	--	pH Modifier	NF	1.06
Water for Injection	Q. S. to 1 mL	--	Vehicle	USP	--
FILLING AID AND BLANKETING AGENT					
Nitrogen Gas (0.2 μ filtered)	Q. S.	--	Filling Aid and Blanketing Agent	NF	--

(PTX-13D at 2).

109. Lupin represented in its ANDA that its product would have "the same active and inactive ingredients in the same concentration" as Lumigan® 0.01% (PTX-13A at 1).

110. As to the pH of Lupin's generic, Lupin's ANDA indicates that it will have a pH in the range of 6.8–7.8. The stability data for one batch of Lupin's proposed bimatoprost 0.01% product shows that the initial pH of Lupin's product was 7.3. The pH was 7.2 after three months.

111. Lupin has also repeatedly stated that its generic product will have the same efficacy and hyperemia profile as Lumigan® 0.01%. For example, Lupin has asked the FDA to let it forgo human clinical trials because the "bioequivalence" of its product and Lumigan® 0.01 % is "self-evident" because they contain the same ingredients in the same amounts (PTX-13A).

iii. Watson's ANDA Filing

112. Watson submitted ANDA 203748 to the FDA seeking approval to market and sell a 0.01% bimatoprost ophthalmic solution. The proposed prescribing information for Watson's product states that it is "for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension" and is to be administered with "[o]ne drop in the affected eye(s) once daily in the evening" (PTX-15A at 1).

113. The label also states that Watson's product is only "0.5 mm Hg less effective" than a 0.03% bimatoprost product (PTX-15A at 8).

114. The composition of Watson's proposed ANDA product is disclosed in the ANDA, which is reproduced in part below:

Ingredients/Grade	Function	Qty (mg/mL)	% w/v
Bimatoprost (In-house)*	Active Ingredient	0.10	0.01%
Benzalkonium Chloride** NF	Antimicrobial Preservative	0.20	0.02%
Sodium Chloride USP	Tonicity agent	7.90	0.79%
Sodium Phosphate dibasic heptahydrate USP (Dibasic Sodium Phosphate Heptahydrate)	Buffering agent	2.70	0.27%
Citric Acid monohydrate USP	Buffering agent	0.14	0.014%
Sodium Hydroxide NF	pH Adjusting Agent	q.s.	---
Hydrochloric Acid NF	pH Adjusting Agent	q.s.	---
Water for Injection USP	Vehicle	q.s.	---
Nitrogen NF	Processing Aid	q.s.	---

(PTX-15D at 3).

115. Watson's ANDA represents that its product will have a pH during its shelf life that ranges from 6.8–7.8 (PTX-15A at 6). Stability testing on test batches indicates that at optimum conditions, the pH is 7.21.

116. Watson has also repeatedly indicated that its proposed product will have the same efficacy and hyperemia profile as Lumigan® 0.01%. Watson asked the FDA for a waiver from conducting human trials, stating that the "*in vivo* bioequivalence" of its product and Lumigan® 0.01% is "self-evident" because they contain "the same active and inactive ingredients in the same concentration" (PTX-15C at 3).

iv. Hi-Tech's ANDA Filing

117. Hi-Tech submitted ANDA 203604 to the FDA seeking approval to market and sell a 0.01% bimatoprost ophthalmic solution. The proposed prescribing information for Hi-Tech's product states that it is "for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension" and is to be administered with "[o]ne drop in the affected eye(s) once daily in the evening" (PTX-12A at 1).

118. The label also states that Hi-Tech's product is only "0.5 mm Hg less effective" than a 0.03% bimatoprost product (PTX-12A at 10).

119. Hi-Tech's ANDA, reproduced in part below, sets out the composition of its proposed product:

Ingredient	*Function*	*Quantity Amount per 1 mL*
Bimatoprost	Active	0.1 mg
Sodium Chloride, USP	Isotonic Agent	8.4 mg
Dibasic Sodium Phosphate Heptahydrate, USP	Buffering Agent	2.56 mg
Citric Acid Monohydrate, USP	Buffering Agent	0.146 mg
Benzalkonium Chloride Solution, NF (50%)	Preservative	0.4 mg*
10% Sodium Hydroxide Solution	To adjust pH	as needed
10% Hydrochloric Acid Solution	To adjust pH	as needed
Purified Water, USP	Vehicle	QS to 1 mL
Nitrogen 97%, NF	To reduce dissolved oxygen	Quantity sufficient

*Equivalent to 0.2 mg of Benzalkonium Chloride, NF per mL

(PTX-12C at 11; Trial Tr. July 26, 2013, Doc. No. 249 at 89:15–23, 91:22–92:8, 95:13–96:23, 98:11–21, 99:18–100:21, 101:16–22.)

120. Hi-Tech's ANDA additionally confirms that its product "contains the same active ingredient, in the same concentration" as Lumigan® 0.01% and that "the inactive ingredients contained in our formulation are the same as" Lumigan® 0.01% (PTX-12B at 1).

121. Regarding the pH of Hi-Tech's generic, Hi-Tech represented to the FDA that its product would have a shelf life pH in the range of 6.8–7.2 (PTX-12A at 9). Batch testing of Hi-Tech's product indicates a pH of 7.0. Hi-Tech represented in its ANDA that "[b]oth the Hi-Tech Pharmacal product (Bimatoprost Ophthalmic Solution, 0.01%) and the Reference Listed Drug Product (Lumigan® (Bimatoporst) Ophthalmic Solution, 0.01%) display very similar physical parameters, such as pH, specific gravity, and osmolality" (PTX-12B at 5).

122. As part of its defense of non-infringement regarding the pH limitation, Hi-Tech argues that there can be no infringement based upon prosecution history estoppel. The original application for the '504 Patent included independent claims with broad concentration ranges for bimatoprost and BAK, but did not include pH limitations. The original application also included narrower dependent claims that included specific requirements for bimatoprost, BAK, and pH. Although the U.S. Patent and Trademark Office (PTO) rejected the broader claims, it concluded that the claims directed to higher concentrations of BAK were patentable because the prior art taught away from these levels of BAK. Therefore, the amendments during prosecution focused upon the patentability of certain concentrations of bimatoprost and BAK, and not on pH limitations. Allergan's changes to pH limitations in the claims during prosecution were tangential to the amendments.

123. Furthermore, Hi-Tech has also repeatedly indicated that its proposed product will have the same efficacy and hyperemia profile as Lumigan® 0.01%. For example, Hi-Tech has asked FDA to grant a waiver from conducting human clinical trials on its product, stating that the product contains the same formulation as Lumigan® 0.01%. Hi-Tech's ANDA assures the FDA that there "would be no difference in the effectiveness of the active drug substance, and one would also observe the same clinical response" when comparing its product to Allergan's Lumigan® 0.01% (PTX-12B at 1).

F. Level of Ordinary Skill in the Art

124. In this case, a person of ordinary skill in the art would be "a person with a scientific degree, either Ph.D., M.D. or B.S., who has at least 2–3 years of experience developing pharmaceutical formulations or treatment methods for the eye or studying or working with bimatoprost and its characteristics or has 2–3 years of experience as a specialist in treating glaucoma, ocular hypertension, and other diseases of the eye, such as an ophthalmologist, who has also assisted in developing ophthalmic pharmaceutical formulations or in designing and running clinical trials on such formulations. This person may also work in collaboration with other scientists and/or clinicians who have experience developing ophthalmic pharmaceutical formulations, running clinical trials related to such formulations, and/or treating patients using such formulations" (Trial Tr. July 18, 2013 Afternoon Session at 28:13–29:5).[3]

G. Scope and Content of the Prior Art

125. The prior art taught several things that undermine the factual premises of Defendants' obviousness case: (1) ophthalmic formulation is a very unpredictable field in

[3] Although the Court adopts Allergan's proposed definition of a person of ordinary skill in the art at the time of invention, the Court's ultimate analysis on infringement and invalidity would remain unchanged had it adopted Defendants' proposal on this issue.

which there are many potential ways for one skilled in the art to modify a product to try to reduce side effects while maintaining efficacy; (2) bimatoprost was known to lose significant IOP-lowering efficacy if its concentration were reduced from 0.03% to 0.01%, thereby teaching away from the claimed invention; (3) the specific dose-response curve for bimatoprost concentration and hyperemia was unknown, making it difficult for the skilled artisan to know how much of a reduction in bimatoprost would be necessary to address hyperemia and whether such a reduction would be possible while maintaining efficacy; (4) the skilled artisan would not have tried to solve the hyperemia problem by quadrupling the amount of BAK because the prior art suggested BAK would not increase the corneal permeability of bimatoprost; and (5) the prior art taught away from increasing the amount of BAK in the formulation to 200 ppm because long-term, chronic use of BAK would cause corneal damage or disorders. The Court discusses each category in detail below.

126. The prior art as a whole strongly discouraged the inventor's approach of significantly increasing the amount of BAK because of the cytotoxic effects of BAK. Importantly, Defendants' expert Dr. John Samples acknowledged that all but one of the prior art references he relied upon to establish obviousness—an article entitled "How to Handle BAK Talk"—had previously been considered by the PTO during prosecution.

i. The Challenges in Ophthalmic Drug Formulation

127. Ophthalmic treatments are often topically applied. But this can lead to formulation complications given the eye's anatomy.

128. The anatomy of the eye presents unique challenges because: (1) a drug formulation administered to the eye has only a very limited time in which it can be absorbed before it is washed away, typically within a minute; (2) the drug must remain

stable after administration for long periods of time; (3) the surface area where the drug may be absorbed is very small; and (4) the eye is very sensitive and is a strong natural barrier that is designed to keep substances out.

129. The problem in this case was exacerbated because Allergan needed to figure out how to disassociate the IOP-lowering effect of bimatoprost from its high instance and severity of hyperemia.

130. The complications in ophthalmic drug formulation are evident by Allergan's surprises during the development of Lumigan® 0.01%. These unexpected results included: (1) that increased concentrations of BAK led to an enormous increase in bimatoprost penetration (especially because the increased concentration of BAK had been included in the testing as a control group, and not as a formulation the inventors expected to enhance penetration); (2) Vitamin E-TPGS—which was included in the emulsion cocktail as a solubilizer—appeared to increase IOP lowering; and (3) Vitamin E-TPGS's apparent enhancement effect did not translate in later testing.

131. The unpredictability is further demonstrated by the Burstein reference. That reference addressed an *in vivo* rabbit study showing 200 ppm BAK improved permeability of fluorescein. But that same amount of BAK did not show any statistically significant improvements in permeation in humans. The drop size in that study was approximately 100 microliters. The drop size for Lumigan® 0.01% is approximately 30 microliters. Therefore, although more BAK was administered to the eye in the Burstein study than with Lumigan® 0.01%, the study showed that BAK did not increase fluorescein permeation in humans.

132. Because of the challenges in ophthalmic formulation, there are a number of approaches that one of skill in the art would have pursued in seeking an improvement to Lumigan® 0.03%. These include: (1) maintaining the same total amount of drug by adding an ingredient—like a cyclodextrin—to complex some of the free drug; (2) adding something to the formulation to selectively block the drug's side effects but not its IOP-lowering activity, such as a calcium borate buffer or a nitric oxide scavenger; (3) reducing the drug concentration but modifying the formulation to keep the drop on the surface of the eye longer, such as by using a gel, gum, suspension, ointment, or nanoparticles; and (4) using a chemical penetration enhancer to increase the absorption of drug into the eye.

133. The Court does not find that ophthalmic drug formulation is a field with a finite number of identified or predictable solutions.

ii. The Prior Art Teachings on Lowering Bimatoprost

134. The prior art—including a 2001 paper by Laibovitz et al. and U.S. Patent No. 6,933,289 (the Lyons Patent)—taught away from decreasing the concentration of bimatoprost. These references taught that decreasing the amount of bimatoprost would result in a decreased IOP-lowering effect.

135. The Laibovitz reference reported a study comparing the safety profile and efficacy of bimatoprost to timolol. The study compared three dosages of bimatoprost, 0.003%, 0.01%, and 0.03%, administered once daily for three weeks and then twice daily for one week, with 0.5% timolol administered twice daily. The results showed that 0.03% bimatoprost had significantly better efficacy than 0.01% bimatoprost. The Laibovitz article reported that 0.03% bimatoprost resulted in approximately 2 mm Hg lowering of IOP more than 0.01% bimatoprost. This is a statistically significant result because the

National Eye Institute conducted research that found that for every millimeter of mercury that eye pressure decreased, patients had a 10% lower chance that their glaucoma would worsen. Therefore, the Laibovitz reference concludes that 0.03% bimatoprost "had the most advantageous overall therapeutic profile" (DTX-151 at 7).

136. The results in Laibovitz showed that 0.01% bimatoprost outperformed timolol. Timolol showed a 12.9% reduction in IOP from the baseline (the typical range reported for timolol was 20–25% from the baseline), whereas 0.01% bimatoprost showed a 20.7% reduction. Laibovitz addressed this as an anomaly, explaining that "[t]he mean reductions from baseline IOP achieved with timolol treatment in this clinical trial were less than anticipated, possible because patients were not excluded for previous use of timolol" (DTX-151 at 4). Allergan's expert Dr. Robert Noecker explained that patients who previously used timolol would achieve tachyphylaxis, where the eyes acclimate to the drug over time and the drug then losses efficacy. Thus, the Court finds that the results in Laibovitz did not indicate that 0.01% bimatoprost would be an encouraging lead even though it lowered IOP more than timolol did.

137. Defendants contend that the efficacy of 0.03% and 0.01% bimatoprost in Laibovitz is closer than 2 mm Hg. Defendants highlight that for once-daily administration, the baseline IOP for 0.01% bimatoprost was 25.2 +/– 0.05 mm Hg and the range of mean changes from baseline was -5.4 to -6.0 mm Hg. For 0.03% bimatoprost, the baseline IOP was 27.0 +/– 0.07 mm Hg and the range of mean changes from baseline was -7.2 to -8.2 mm Hg. Defendants believe that since the overall end values for both groups are nearly equivalent, the two concentrations of bimatoprost are equally efficacious. The Court disagrees. Because of the complexities associated with the

statistical calculations, the Court finds that the end values are not comparable or meaningful to the analysis in Laibovitz.

138. Turning to the Lyons Patent, this reference discloses that "[c]linical trials have shown that 0.02% bimatoprost shows little hyperemia, but also loses efficacy" (DTX-71 at 12:30–31). The patent repeatedly discloses that the preferred concentration is 0.03% bimatoprost. Therefore, the Lyons Patent discloses addressing hyperemia by adding a cyclodextrin to complex with bimatoprost and reducing the free bimatoprost available to cause hyperemia while also adding a viscosity agent to keep the formulation on the eye longer to maintain efficacy. Accordingly, the Lyons Patent teaches away from trying to reduce the total amount of bimatoprost and instead suggests keeping the total bimatoprost concentration at 0.03% to avoid losing efficacy while making other changes to the formulation to address hyperemia. Although the patent discloses the use of 0.01% bimatoprost, it also requires the additions of a cyclodextrin and a viscosity enhancer. Even at the 0.01% bimatoprost concentration, the patent does not represent that it is as effective as 0.03% bimatoprost. Instead, the opposite is true.

139. The Lyons Patent additionally states that "it is preferable that the concentration of free (uncomplexed) bimatoprost is less than 0.02%" (DTX-71 at 7:37–39). The Court does not find this statement to refer to the total concentration of bimatoprost. Rather, it refers to the amount of free bimatoprost remaining—after permeation—that could cause hyperemia.

140. Based upon the Laibovitz paper and the Lyons Patent, one of ordinary skill in the art would have looked at solutions other than lowering the concentration of bimatoprost

from 0.03%. To the extent bimatoprost was lowered to 0.01%, a person of ordinary skill in the art would have expected the formulation to lose efficacy in lowering IOP.

iii. Dose-Response Curve for Bimatoprost and Hyperemia

141. Nowhere in the prior art is it disclosed that a concentration reduction in bimatoprost causes a reduction in the frequency or severity of hyperemia.

142. The Laibovitz paper actually teaches that a reduction in bimatoprost concentration from 0.03% to 0.01% does not result in reduced hyperemia. In that study, more patients in the 0.01% bimatoprost group (15%) experienced conjunctival hyperemia than did patients in the 0.03% bimatoprost group (5%). And the two groups showed similar severity of hyperemia. The mean range of hyperemia scores for patients in the 0.01% bimatoprost group were 0.85 to 0.95, while mean scores for patients in the 0.03% group were 0.80 to 0.98. Therefore, Laibovitz teaches a person of ordinary skill in the art that a reduction in bimatoprost from 0.03% to 0.01% does not reduce the frequency or severity of hyperemia.

143. This data is consistent with what one of ordinary skill in the art would have appreciated about drug formulation and dose-response curves. Dose-response curves for efficacy and side effects vary from drug to drug. It is not uncommon for a reduction in dose concentration to have no impact on side-effect reduction.

144. The Lyons Patent does not disclose a specific dose-response curve for bimatoprost and hyperemia. But Defendants highlight that the patent discloses that "[c]linical trials have shown that 0.02% bimatoprost shows little hyperemia" (DTX-71 at 12:30–31). But the Lyons Patent provides no details regarding the frequency or severity that could be expected with a 0.02% bimatoprost formulation. Furthermore, the reference gives no comparison to the efficacy of 0.03% bimatoprost. The Lyons Patent sought to

remove free bimatoprost from the ocular surface; it did not attempt to reduce hyperemia via reduced bimatoprost concentrations. In light of Laibovitz, a person of ordinary skill in the art looking at the Lyons Patent would have no guidance as to whether a reduction from 0.03% to 0.01% bimatoprost would result in decreased frequency or severity of hyperemia.

iv. BAK as a Permeation Enhancer

145. The prior art does not teach one of ordinary skill in the art that high concentrations of BAK would enhance the corneal penetration of bimatoprost. A person of ordinary skill in the art would not—based upon the prior art—appreciate that quadrupling the concentration of BAK from 50 ppm to 200 ppm would counteract a reduction of bimatoprost from 0.03% to 0.01% and result in equivalent efficacy but an improved hyperemia profile.

146. Regarding the prior art teachings of increased bimatoprost concentrations, the Court finds that: (1) the only prior art that reports data on the effect of BAK on bimatoprost's IOP-lowering effect suggested that increasing the amount of BAK would have no effect; (2) the prior art that examined prostaglandin-analog molecules that were most similar to bimatoprost—the Higaki and Camber articles—showed that BAK actually inhibited their corneal penetration; and (3) Defendants' prior art showing increased BAK concentrations is inadequate because (i) it dealt with active drugs that are molecularly dissimilar to bimatoprost, (ii) it did not report any meaningful results in humans, and (iii) it repeatedly warned about the potential risks and toxicological complications of using increased BAK.

a. Prior Art Does Not Show that Increased BAK Increases Corneal Penetration

147. A study that was a part of the Medical Review published by the FDA on Lumigan® 0.03% compared the results of 0.03% bimatoprost preserved with BAK to 0.03% bimatoprost non-preserved. Based upon the formulation numbering, the data in the Medical Review, and the publically available information on the label for Lumigan® 0.03%, one of ordinary skill in the art would have understood that the preserved formulation included 50 ppm BAK while the non-preserved formulation did not include any BAK. But because the other ingredients in the formulations were redacted by the FDA prior to publication, one of ordinary skill in the art would not have known what else was included in the formulations.

148. The results of the study demonstrate that the formulation with 0.03% bimatoprost with 50 ppm BAK and the formulation with 0.03% bimatoprost with no BAK achieved equivalent IOP lowering.

149. The FDA reviewer commented that "[t]here is not a clear separation in IOPs between the active treatment groups until Day 29 Hour 12 when the greatest IOP lowering effect is demonstrated by 0.03% [non-preserved]" (PTX-213 at 112). For comparison purposes, at the end of the 29-day study, 0.03% bimatoprost with BAK lowered mean IOP from the baseline by -5.92 mm Hg while 0.03% bimatoprost without BAK lowered mean IOP from the baseline by -7.31 mm Hg.

150. Accordingly, this study teaches one of ordinary skill in the art that BAK does not function as a permeation enhancer for bimatoprost. The teachings in this study are corroborated by the thoughts of Allergan's scientists that increased BAK would not be a promising approach in human trials.

151. Even though the main goal of the Medical Review study was to investigate IOP lowering in humans, the data on permeation is informative. The purpose of the invention was to create a formulation that maintained the same IOP-lowering effect as Lumigan® 0.03% in humans. It would have been immaterial if BAK increased ocular penetration if that increased penetration did not also result in greater IOP-lowering efficacy. The FDA Medical Review results focus on lowering IOP, meaning that they speak to the exact issue addressed by the claimed invention.

152. At trial, Defendants indicated that the 0.03% bimatoprost non-preserved formulation contained poloxamer 407, which was not included in the preserved formulation. At the time of publication of the Medical Review, a person of ordinary skill in the art would have no means of obtaining that information. Furthermore, there is no evidence that poloxamer 407 would actually change the amount of IOP lowering observed with the non-preserved formulation. In fact, inventor Scott Jordan's August 2004 e-mail explicitly addresses that the unpreserved formulation contained poloxamer, but also indicates that the study described in the FDA Medical Review made him skeptical that BAK would enhance bimatoprost's ocular penetration in humans. This contemporaneous evidence from near the time of invention shows that a person of ordinary skill in the art at the time would not have thought that poloxamer would impact the results.

153. The Court has considered Defendants' argument that a January 2010 Allergan document indicated that "a definitive conclusion could not be made" about the relative IOP lowering of the preserved and unpreserved formulations due to the presence of poloxamer (DTX-720). But this argument is not persuasive because the January 2010

document was written years after the invention and because the mere fact that a "definitive" conclusion could not be made does not undermine the teachings of the study. The Court finds that the contemporaneous interpretation of the study from Mr. Jordan's August 2004 email more accurately reflects what the study results would have taught one skilled in the art at the relevant time.

154. Ultimately, the Court finds that the FDA's Medical Review taught away from increasing the concentration of BAK as a permeation enhancer for bimatoprost.

b. BAK Inhibited Penetration of Prostaglandin Analogs Similar to Bimatoprost

155. Two references—the Higaki reference and the Camber reference—address the impact of BAK on prostaglandin-analog drugs. The Court finds that both of these references teach that BAK would decrease the permeation of a prostaglandin-analog drug, like bimatoprost. Additionally, the use of increased BAK in Xalatan® would not have taught one of ordinary skill in the art to use BAK as a penetration enhancer.

156. The 1996 Higaki paper studied the effects of BAK on corneal penetration of S-1033 acid, a prostaglandin-derivative and S-1033 methly ester. The Higaki study determined that although BAK improved the corneal permeability of S-1033 acid, it reduced the permeability of S-1033 methyl ester. One skilled in the art would have recognized that S-1033 acid is a charged molecule at physiological pH (approximately pH 7), while S-1033 methyl ester is a neutral molecule. One skilled in the art also would have known that bimatoprost was a neutral molecule, both at the time of administration and throughout the course of its pharmacological activity in the eye. Accordingly, a person of ordinary skill in the art would have concluded that BAK would inhibit—rather than promote—corneal penetration of bimatoprost. Therefore, this reference teaches away from using BAK as a penetration enhancer for bimatoprost.

157. At trial, Defendants took the log P value calculated by Allergan for bimatoprost and compared it to the log P values in figure four of the Higaki reference (DTX-183 at 8). Based upon a regression curve, one can compare log P values to determine the expectation that a particular molecule will have enhanced corneal penetration with BAK. The Court finds Defendants' comparison inherently flawed. Initially, the log P taken from Allergan's documents would not have been available to a person of ordinary skill in the art at the time of the invention. Additionally, in order to compare log P values on the same regression curve, the values must all be calculated using the same methodology. Log P values can be calculated experimentally or by computer software. But the log P value calculated under one methodology differs considerable when calculated via other methods or parameters. Therefore, for purposes of comparison on a single regression curve, the data must come from the same methodology. No evidence supports that the methodology in the Higaki reference for calculating log P values is identical to the methodology used by Allergan. Defendants also do not do an independent analysis of all the log P values using a single method.

158. The 1987 paper by Camber and Edman addressed the "[f]actors influencing the corneal permeability of prostaglandin $F_{2\alpha}$ and its isopropyl ester *in vitro*" (PTX-90 at 1). The Camber reference reported that the addition of BAK decreased the corneal permeability of $PGF_{2\alpha}$ isopropyl ester, while increasing the permeability of $PGF_{2\alpha}$, which is an acid. The data established that adding 100 ppm BAK resulted in a nearly 50% reduction in the permeability coefficient for the isopropyl ester. As Camber teaches, a person of ordinary skill in the art would have the knowledge that $PGF_{2\alpha}$ is a charged molecule and that $PGF_{2\alpha}$ isopropyl ester is a neutral molecule. As previously addressed, a

person of ordinary skill in the art would have also understood that bimatoprost was a neutral molecule. As Allergan's expert Timothy McDonald explained at trial, the charge of a molecule is one of the most important features for determining permeability of molecules passing through the lipophilic corneal membrane. Therefore, the Camber reference teaches that BAK would not increase permeability for neutral molecules (including bimatoprost). In fact, Camber teaches that the administration of BAK with a neutral drug would inhibit ocular penetration.

159. Xalatan® was a competitor to Lumigan® 0.03%. The active drug ingredient in Xalatan® is latanoprost. A Canadian patent (the Asada reference) discloses that Xalatan® uses BAK in increased concentrations. In fact, Xalatan® contains 200 ppm BAK. Although Xalatan® uses increased concentrations of BAK, the Asada reference does not teach that it was used as a penetration enhancer. BAK has no penetration enhancing benefits for latanaprost. Instead, BAK is included in high concentrations in Xalatan® because it prevents precipitate from salting out of solution. If lower concentrations of BAK are used, then white solids form in the product, making it unacceptable for ocular administration. Therefore, the majority of BAK in solution complexed with latanaprost and was not free in solution to interact with the epithelial cells. The purpose of BAK in Xalatan® was to keep the solution dissolved, rather than act as a penetration enhancer. Furthermore, the Asada reference explains that although "BAK is the excellent preservative, it may cause the corneal disorders when used at the high concentration. Accordingly, when BAK is added to the ophthalmic solution, it is desirable to lower its concentration as low as possible" (DTX-22 at 7). The Asada reference teaches that preferred concentrations of BAK range from 30–100 ppm.

160. A 2006 research abstract looked at the influence of BAK on the permeation of latanaprost into rabbit aqueous humor. The abstract states that "[b]enzalkonium chloride (BAK) is a most-used preservative in ophthalmic solutions, however, it is well-known that a high concentration of BAK might lead to corneal disorder. The purpose of this study is to evaluate the influence of BAK in latanoprost ophthalmic solution on the penetration of latanoprost into rabbit aqueous humor, and the possibility of reducing the BAK concentration in the product" (PTX-110). The authors tested latanoprost formulations with 200 ppm BAK, with less BAK, and with no BAK. The study concluded that "[t]he BAK concentration in latanaprost ophthalmic solution did not affect [*sic*] on the penetration of latanaprost into rabbit aqueous humor after a single ocular instillation" (PTX-110). In light of this result, the study concluded that a "reduced BAK concentration should be available for the latanaprost ophthalmic solution" (PTX-110). Although this abstract was published after the invention date, the Court notes that it is consistent with the teachings in Higaki and Camber that BAK does not enhance the penetration of neutral molecules, such as latanoprost. Therefore, one of ordinary skill in the art would again conclude that BAK did not function as a penetration enhancer of neutral prostaglandin-analog compounds, including bimatoprost.

c. Defendants' Cited Prior Art is Inadequate

161. During trial, Defendants raised several pieces of prior art to show that a person of ordinary skill in the art would have recognized that BAK would be a penetration enhancer for bimatoprost. The Court disagrees. The Court finds that the prior art cited by defendants does not teach BAK as a penetration enhancer for bimatoprost and also does not teach that if BAK were increased with bimatoprost, the resulting product would remain as efficacious as Lumigan® 0.03%. Although the Court highlights several of

Defendants' prior art below, the Court notes that in considering all of the evidence, the prior art is inconsistent with Defendants' position.

162. A 1986 review paper by Vincent Lee looks at a number of methods for improving ocular drug delivery systems. Part of the reference states that "[b]enzalkonium chloride and other cationic surfactants are probably the most popular preservatives in ophthalmic solutions. By altering integrity of the corneal epithelium, these surfactants have been found to enhance the ocular absorption of a variety of drugs varying in molecular size and lipophilicity, including pilocarpine, prednisolone, homatropine, inulin, and horseradish peroxidase" (DTX-185 at 7 (citations omitted)). Although the reference teaches that BAK could be used to increase penetration of certain molecules, those molecules are all readily distinguishable from bimatoprost. As the experts identified at trial, there are a number of factors that influence permeability, including whether the compound is charged or neutral, the size of the molecule, the molecular structure of the compound, and whether the compound is hydrophilic (water-loving) or lipophilic (fat-loving). Pilocarpine and carbachol are both charged molecules, and behave very differently than bimatoprost, a neutral molecule. Insulin and horseradish peroxidase are two very large hydrophilic compounds that would behave differently than bimatoprost, a small lipophilic compound. The remaining compounds of prednisolone and homatropine are both 150 to 200 times less lipophilic than bimatoprost, and therefore behave considerably differently. Given bimatoprost's properties, the Lee reference does not disclose how BAK would impact its permeability. Overall, the Lee reference did not give any information regarding prostaglandin molecules.

163. The Lee reference also explains that "[a] drawback of this approach is the possibility of accumulation of surfactants within the eye resulting in unknown toxicological complications, as exemplified by benzalkonium chloride" (DTX-185 at 7 (citations omitted)). The reference concludes that "[o]verall, the mechanisms by which these inert ingredients affect ocular drug bioavailability are only begun to be understood. Further work is necessary to determine if any of these ingredients can be safely used to optimize the ocular bioavailability of certain drugs while achieving their primary goal of preserving product stability and sterility" (DTX-185 at 7). The Lee reference was published prior to either Higaki or Camber. In light of the subsequent findings in Higaki and Camber, a person of ordinary skill in the art would not have thought that BAK would increase permeation of bimatoprost. In light of the known toxic effects of BAK, the reference actually cautions against its use. The Lee reference itself recognizes that any increased permeability seen by BAK may be a result of its adverse effects on the eye, specifically, compromising the integrity of the corneal epithelial barrier. In this regard, Lee states that "the usefulness of this approach to enhance corneal absorption is questionable" (DTX-185 at 24). In total, the Court does not find that the Lee reference discloses the use of BAK to increase bimatoprost permeability.

164. A 1980 article by Keller et al. discloses increased permeability of inulin in rabbits using 200 ppm BAK. Although this reference teaches the use of higher concentrations of BAK to increase inulin permeation, the Court does not find the results translate to using BAK to enhance bimatoprost penetration. As an initial matter, inulin is a very large and hydrophilic molecule, characteristics dissimilar from bimatoprost. Furthermore, inulin is not a prostaglandin, but a sugar molecule derived from the chicory root. The study states

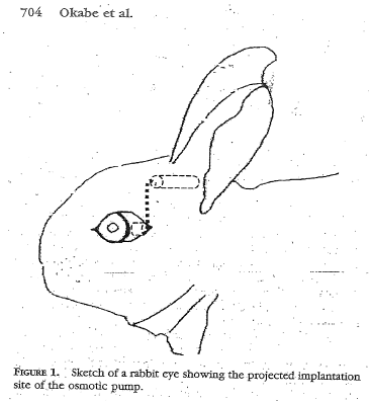
that "[i]nulin was used because this molecule, due to its relatively large size (mol. wt. 5000), has virtually no capacity to penetrate an intact corneal epithelium" (DTX-184 at 4). Therefore, the Keller article does not teach anything about BAK's potential impact on bimatoprost's permeability, especially given that prior art addressing other prostaglandin taught away from the claimed invention. Furthermore, any permeability caused by BAK for inulin is likely due to its harmful effects. The reference states that "[s]tructural changes in the epithelium due to benzalkonium chloride have been shown. At 5 to 15 min after instillation of 0.01% BAC in vivo, cell damage and separation are observed in the superficial layers of the corneal epithelium" (DTX-186 at 9).[4] Ultimately, the reference concludes that "[i]n vitro and in vivo studies of the deleterious effects of BAC solutions on the cornea indicate that eyedrops containing BAC should be used with caution in the treatment of at least some eye conditions" (DTX-186 at 10). Nowhere does the reference suggest increasing BAK would benefit bimatoprost penetration. The Court finds that a person of skill in the art would not have found the Keller reference encouraging. In fact, Keller teaches away from using BAK at concentrations over 100 ppm BAK due to potential damage to the corneal epithelium cells.

165. Defendants also highlight a 2002 non-peer reviewed article titled "How to Handle BAK Talk" to support their assertion that BAK was a known penetration enhancer. The reference addresses prior studies involving beta blockers and peptides, both of which are structurally dissimilar from bimatoprost and other neutral prostaglandin analogs (DTX-741 at 1). The reference provides no data or explanation of under what circumstances BAK will enhance penetration. In light of Higaki, Camber, and the FDA's Medical

[4] Although the Court uses BAK to identify benzalkonium chloride, another common notation for the preservative is BAC.

Review, a person of ordinary skill in the art would have continued to recognize that BAK was not a penetration enhancer for bimatoprost.

166. A February 2005 article (the Okabe reference) considers the impact of BAK on the scleral permeability of betamethasone-21-phosphate. The reference states that "[t]he results of this study demonstrate that BAK may improve the ocular penetration of a drug in a transscleral drug delivery system without producing toxic reactions" (DTX-308 at 2). But betamethasone-21-phosphate is a charged molecule that is considerably more hydrophilic than the neutral lipophilic compound bimatoprost. Furthermore, the reference does not disclose any suggestion of using BAK with prostaglandin analogs. Additionally, the drug delivery system in the Okabe reference was considerably different than with bimatoprost application. Bimatoprost is administered to the human eye in eye drops. In Okabe, the drug was delivered to the eye of rabbits using an osmotic pump that was implanted in the rabbit as follows: "[a]fter the sclera was exposed, a sclera pocket was made with a crescent knife 2 mm from the limbus at half the depth of the total scleral thickness. . . . The osmotic pump was implanted subcutaneously. A silicone tube connected to the osmotic pump was placed in the scleral pocket and sutured with 7-0 silk (Fig. 1)" (DTX-308 at 3). Figure one from the reference is reproduced below as illustration:



(DTX-308 at 3). This delivery system is not comparable to the eye drop delivery system for bimatoprost. As previously addressed, results seen in animal testing are not guaranteed to translate to human testing. The Court finds that a person of ordinary skill in the art would not have found the Okabe reference to teach anything about whether BAK could increase bimatoprost's permeability in a live human.

167. A 2002 article (the Ke reference) studies the use of penetration enhancers and viscosity enhancers to improve the bioavailability of the antibiotic ciprofloxacin. The study found that the use of a penetration enhancer and a viscosity enhancer overcame penetration barriers and loss due to wash-out. This resulted in increased penetration of the drug. But the permeation-enhancing compound studied in this case was dodecylmaltoside, not BAK. The Ke reference is actually critical of the use of BAK. It states that "high concentrations of BAC or anesthetics can be toxic to the eye" (DTX-339 at 2). This reference merely provides an alternative preservative that might have penetration-enhancing capabilities. A person of ordinary skill in the art would gather no information regarding BAK or bimatoprost from this reference.

168. Defendants' expert Dr. Soumyajit Majumdar also indicated that the nasal spray Miacalcin uses BAK as a penetration enhancer. But drug delivery via nasal administration versus ophthalmic administration is markedly different because they are different organs. Defendants presented no evidence that would suggest that BAK would behave similarly in these two different areas of the body and made no showing that the active ingredient in Miacalcin would be structurally similar. Defendants did not demonstrate that the active ingredient in Miacalcin has some characteristic that would

teach that BAK would enhance bimatoprost's permeability, especially when all of the prior art addressing prostaglandin analog taught the opposite.

169. Defendants' expert Dr. Majumdar stated that although bimatoprost is a lipophilic molecule, it behaves like a hydrophilic compound, and therefore a good candidate for BAK absorption enhancement. Dr. Majumdar looked at a 2004 article by Krauss et al. (DTX-210) and a 2001 article by Tak et al. (DTX-343) to reach this conclusion. Specifically, he reaches his conclusion using data on bimatoprost's scleral and corneal penetration rates from the Krauss reference and comparing them to data from the Tak reference, which addresses the penetration rates of the molecules mannitol and diazepam. But Dr. Majumdar agreed that nothing in the literature supports categorizing bimatoprost as a hydrophilic compound. Bimatoprost permeates the eye via both the cornea and sclera. The fact that its scleral penetration rate is approximately four times faster than its corneal penetration rate does not mandate a conclusion that the compound behaves like a hydrophilic molecule. Dr. Majumdar could point to no evidence as to why bimatoprost does not have better corneal—or for that matter scleral—penetration. Accordingly, the Court finds Dr. Majumdar's position without merit.

170. The Court does not find that any of Defendants' prior art teaches or suggests that BAK would enhance the penetration of bimatoprost or that the person of ordinary skill in the art should try such an approach or would have a reasonable expectation of success.

v. The Prior Art Teachings on Increasing BAK Concentrations

171. The Court additionally finds that the prior art taught away from increasing the BAK concentration to 200 ppm with bimatoprost. BAK is a known cytotoxin (i.e., an agent that kills cells), so the prior art taught to minimize the use of BAK in ophthalmic formulations. BAK was known to be an irritant and associated with hyperemia. Thus,

increasing its concentration would exacerbate the hyperemia problem. Defendants' own experts previously cautioned against the use of BAK because of its side-effect profile. Additionally, the Court finds Defendants' reliance on products with increased BAK concentrations misplaced. The Court addresses each issue in more detail below.

a. BAK Causes Cellular Damage

172. Defendants' expert Dr. John W. Samples confirmed that a person of ordinary skill in the art would have known as early as 1983 of the toxic effects of BAK in the eye.

173. Dr. Samples agreed regarding the concerns about the long-term effects of BAK administration and that "it is possible that the basic function of the trabecular meshwork may become impaired as a result of chronic benzalkonium exposure" (Trial Tr. July 17, 2013 Morning Session at 79:19–21).

174. Dr. Samples also explained that one of the concerns of BAK was that it was harming the function of the trabecular cells in the eye. These cells are responsible for the fluid outflow from the eye. In harming these cells, BAK would therefore impair that draining system. The result would be increased IOP. This result mimics the effects of open angle glaucoma.

175. Dr. Samples further agreed that another concern of BAK was "its role in and contribution to dry eye conditions. This is a particular concern because dry eye conditions and ocular surface disease are particularly common in glaucoma patients" (Trial Tr. July 17, 2013 Morning Session at 84:1–4).

176. Dr. Samples confirmed that the toxicological effects of BAK were widely known in the field. Exemplary of this is a 2004 article by Dr. Noecker explaining that "1-month treatment with glaucoma medications containing higher levels of BAK resulted in more

corneal damage and conjunctival lymphocytic infiltration than lower levels of BAK" (PTX-163 at 7).

177. Dr. Samples also agreed that the effects of BAK are dose dependent. Increasing the dose of BAK also increases the instance and severity of its negative effects, in this case the damage to ocular epithelial cells.

178. Dr. Samples confirmed that BAK's negative effect is universal for all cells, including "corneal, epithelium, and endothelium conjunctival epithelium, and trabecular meshwork cells" (Trial Tr. July 17, 2013 Morning Session 87:21–22).

179. Given BAK's toxicity, Dr. Samples concluded that "clinicians should consider the total amount of BAK included in each of their patient's glaucoma treatment regimens. This is especially critical if multiple BAK-containing medications are prescribed simultaneously" (Trial Tr. July 17, 2013 Morning Session 88:6–10). At the time of invention, it was understood that many glaucoma patients were on multiple treatments and therefore subject to the cumulative degenerative effects of BAK.

b. The Prior Art Taught that BAK Should be Minimized in Ophthalmic Formulations

180. Given BAK's ophthalmic toxicity, the prior art taught that BAK should be minimized in ophthalmic formulations.

181. Dr. Samples and Dr. Noecker agreed that a goal in ophthalmology is to eliminate BAK as a preservative in all ophthalmic formulations. To the extent it could not be eliminated, the experts agreed that its use should be minimized.

182. Dr. Chin-Ming Chang of Allergan was one of the lead formulators on the Lumigan® 0.01% project. He explained that "using less preservative is the gold standard for the formulation development" and agreed that the least amount of BAK present would

be the most beneficial formulation (Trial Tr. July 15, 2013 Afternoon Session 40:19–20). Dr. Chang also explained that a person of skill in the art would not have increased the amount of BAK in a formulation "because we know that the minimum amount of preservative need[s] to be utilized, not only from a scientific perspective, but also from a regulatory perspective" (Trial Tr. July 15, 2013 Morning Session 78:15–18). A person of ordinary skill in the art at the time would have feared that "BAK increased the ocular penetration purely by compromising cell layer integrity and toxicity" (Trial Tr. July 15, 2013 Morning Session 81:15–17).

183. Dr. Noecker noted three industry examples of products reformulated to decrease the concentration of BAK. The drugs Alphagan® and Travatan® both eliminated BAK while Acular® reduced its concentration of BAK. Conversely, neither party identified any product reformulated to increase its concentration of BAK.

c. A Person of Skill in the Art Would Not Use BAK to Reduce Hyperemia

184. Dr. Loftsson stated that a person of ordinary skill in the art would not use BAK to reduce hyperemia because BAK itself leads to hyperemia.

185. Dr. Samples highlighted two examples where elimination of BAK resulted in decreased hyperemia: Travatan Z® and Alphagan P®. In those products, other preservatives were substituted for BAK. As a result, both showed lower rates of hyperemia.

186. Although bimatoprost is the leading cause of hyperemia in Lumigan®, a person of ordinary skill in the art would not have increased the concentration of BAK for purposes of eliminating hyperemia.

d. Defendants' Experts Cautioned Against the Use of BAK

187. Defendants' experts at trial recounted their prior statements regarding BAK and discouraging its use.

188. Defendants' expert Dr. Samples—prior to the instant litigation—wrote in his book on glaucoma that "BAK contributes greatly to symptoms of ocular surface disease experienced by many glaucoma patients" (Trial Tr. July 17, 2013 Morning Session 113:24–114:1). Dr. Samples has also previously written that "[i]t has been argued that BAK has some anti-infective roles or that BAK is somehow desirable to perform penetration of antibiotics" (Trial Tr. July 17, 2013 Morning Session 114:7–9). But Dr. Samples goes on to warn a person of ordinary skill in the art that "such arguments ignore the cellular consequences associated with the use of preservatives" (Trial Tr. July 17, 2013 Morning Session 114:14–16).

189. These consequences are highlighted in the 2002 Kaur et al. article. Although the article states that BAK "shows the highest promoting effect on corneal drug penetration from amongst the currently used preservatives" it goes on to explain the negative consequences of BAK that caused that permeability (DTX-286 at 7). Specifically, that "0.01% BAC has been reported to cause cells of the corneal epithelium to peel at their borders" and "enlarge the intercellular spaces in the superficial cells of the cornea" (DTX-286 at 8). Dr. Samples agreed these consequences naturally flow from the use of BAK. Dr. Samples confirmed that the removal of the "grout" between the cells increases permeability, but is the result of BAK's damaging effects as a "grout-dissolver" (Trial Tr. July 17, 2013 Morning Session at 36:25, 37:2).

190. Similarly, Dr. Majumdar authored an article in 2006 stating that although the approach of using surfactants as permeation enhancers "was initially received with a lot

of enthusiasm, cytotoxic and membrane damage properties at the concentrations necessary to produce sufficient permeability enhancement has limited their utility in drug delivery" (Trial Tr. July 17, 2013 Afternoon Session 151:10–14). Dr. Majumdar's comments help establish that one of ordinary skill in the art would have been discouraged that increased BAK—because of its cytotoxic effects—would promote permeation.

191. The prior statements by Defendants' experts confirm that one skilled in the art at the time of invention would not have tried to use BAK as a penetration enhancer given its toxicity profile.

e. Defendants' Reliance on Products with Increased BAK

192. As previously addressed, Xalatan® contained 200 ppm BAK for the purpose of keeping the latanaprost dissolved, not for permeation enhancement. The increased BAK complexed with latanaprost, therefore reducing the amount of free BAK to interact with the eye. Like the Asada reference, both Dr. Samples and Dr. Noecker agree that Xalatan® "showed a decrease in cell membrane integrity and a significant increase in apoptosis [i.e. targeted cell death]" when compared with another prostaglandin with 50 ppm BAK (Trial Tr. July 17, 2013 Morning Session 103:13–14). Dr. Noecker's 2004 article confirms this and discloses that "[b]imatoprost, which contains the lowest BAK concentrations of the evaluated medications (0.005%) [50 ppm], was associated with less damage than latanoprost, timolol, or dorzolamide" (PTX-163 at 6). As Dr. Samples and Dr. Noecker agree, Xalatan® was the only chronically used FDA-approved ophthalmic drug that included 200 ppm BAK as of 2005. And its use taught away from increased BAK concentrations for the reasons already discussed. Given the experts' statements, a person of ordinary skill in the art would have sought to not to increase the amount of BAK in Lumigan®. The Court finds that these references teach away from using

prostaglandin analogs with an increased BAK concentration, which increase the risk of corneal damage.

193. During trial, Defendants repeatedly highlighted the 2002 article "How to Handle BAK Talk" (DTX-741). In this reference, Defendants emphasized several formulations including 200 ppm BAK. These drugs include Natacyn, Decadron phosphate, and Neodecadron. Natacyn, Decadron phosphate, and Neodecadron are not for chronic long-term use, and would teach nothing about whether it was safe to use 200 ppm BAK with a lifelong glaucoma drug. The "How to Handle BAK Talk" reference states that "BAK may enhance a drug's ability to reach the site of action, and it can increase ocular permeability" (DTX-741 at 3). But it goes on to explain that its use comes with complications, "[t]here can be damage to the ocular surface if use of the drop becomes too frequent for a long period of time or if several preserved topical ophthalmic medications are used daily" (DTX-741 at 3). For example, Natacyn is used as treatment for patients who have fungal infections in their eyes. Natacyn is an extremely toxic agent because it kills the fungus eating at the eye as well as some surface cells. Therefore, Natacyn use is limited to only when a fungus is present. Decadron phosphate and Neodecadron are both steroid preparations used for short-term treatment of inflammation. In light of the short-term use of the drugs identified by Defendants, this reference does not teach that BAK in increased concentrations would be promising for chronic or long-term use.

194. Defendants also pointed to Xalacom as safely using 200 ppm BAK. Xalacom includes latanaprost as one of its active ingredients. As previously discussed, latanaprost

and BAK complex in solution and reduce the amount of free BAK. Under these circumstances, BAK in increased concentrations is not acting as a permeation enhancer.

195. Defendants also addressed the previous research done by Allergan's expert Dr. Thorsteinn Loftsson. Dr. Loftsson previously used 200 ppm BAK with cyclodextrins. But at trial, Dr. Loftsson explained that "[i]f you use cyclodextrin together with a preservative, you will reduce the amount of free preservative in your formulation, so only a small fraction of your preservative is able to interact with the bacteria and have this antibacterial effect" (Trial Tr. July 18, 2013 Afternoon Session 76:23–77:2). This research does not teach that 200 ppm BAK in one formulation means that concentration is universally recommended for all formulations, regardless of ingredients. This is especially true when the preservative complexes in the product.

196. Consequently, the Court finds that the prior art as a whole taught away from increasing the concentration of BAK from 50 ppm to 200 ppm in an ophthalmic formulation of prostaglandin analogs.

H. Difference Between Prior Art and the Claims

197. Although Defendants did not explicitly compare the prior art to the claims, the Court finds it prudent to do so. Overall, the Court finds there are meaningful differences between the prior art and the claims.

198. The Court does not find that that the prior art teaches a formulation of 0.01% bimatoprost with 200 ppm BAK.

199. The prior art also does not teach that a formulation of 0.01% bimatoprost and 200 ppm BAK would have equivalent efficacy in lowering IOP as 0.03% bimatoprost and 50 ppm BAK.

200. The prior art does not teach that BAK would act as a permeation enhancer for bimatoprost.

201. The prior art does not teach that increasing the BAK to 200 ppm would be safe or desirable given its toxicity profile.

202. The Court also does not find that there would have been a reason or motivation for a person of ordinary skill in the art to combine the prior art or choose specific concentrations of bimatoprost and BAK to arrive at the claimed invention. The prior art taught that BAK would not enhance bimatoprost penetration and that decreasing the bimatoprost concentration from 0.03% to 0.01% would decrease efficacy in IOP lowering. As detailed above, Allergan spent over two years pursuing other solutions. This is true even though Allergan was aware of data that BAK was a penetration enhancer for some drugs under limited conditions. The Court finds that the inventors' contemporaneous efforts are probative of how one of ordinary skill in the art would have approached the problem at the time. The Court also does not find that Allergan's motivation to solve the hyperemia problem with Lumigan® 0.03% equates to motivation for combining the prior art to reach the ultimate invention. Although there was a desire to develop an improved formulation of Lumigan® 0.03%, no evidence indicates that a person of skill in the art would have known how to fulfill that goal.

203. The Court finds that in view of the prior art, there was no reasonable expectation of success in making the claimed invention. Looking at the Laibovitz reference and the Lyons Patent, a person of ordinary skill in the art would not have expected that a formulation containing 0.01% bimatoprost would have been able to maintain the IOP-lowering efficacy of 0.03% bimatoprost. The inventors themselves remained skeptical of

a formulation of 0.01% bimatoprost even after their initial research. Similarly, a person of ordinary skill in the art would not have known whether reducing the concentration of bimatoprost to 0.01% would have reduced the hyperemia seen with Lumigan® 0.03%. A person of ordinary skill in the art would not have expected that BAK would increase the corneal penetration of bimatoprost, given that the prior art taught away from the invention and demonstrated that BAK did not increase the permeability of many compounds, including bimatoprost and other neutral prostaglandin analogs.

I. Objective Indicia of Non-Obviousness

204. The Court finds that the objective considerations also counsel against a finding that a person of ordinary skill in the art would have found the invention obvious.

205. Allergan released Lumigan® 0.03% in 2001. Although the drug reduced IOP, it caused high instance and severity of hyperemia. This often caused patients to discontinue treatment. In March 2005—when Allergan filed its patent application for the instant invention—there existed a long-felt need for a glaucoma drug with Lumigan® 0.03%'s efficacy, but with an improved side-effect profile, including decreased instance and severity of hyperemia. The 1996 Higaki article exemplifies this point. The Higaki reference explains that:

> [A] new type of antiglaucoma medication is needed. One candidate has been prostaglandin because prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and E_2 (PGE_2) have long-lasting and highly significant activity for decreasing intraocular pressure. However, they also have several adverse effects which must be overcome before they can be clinically used; they can cause initial hypertension, inflammatory response, breakdown of the blood-aqueous barrier, and systemic side effects.

(DTX-183 at 3 (citations omitted)). Defendants contend that Allergan developed Lumigan® 0.01% to extend its patent monopoly on bimatoprost. The Court disagrees.

Allergan immediately began research into improvements on Lumigan® 0.03% to develop an improved drug with decreased side effects. Dr. Samples agreed that eliminating hyperemia would have been a paramount concern with Lumigan® 0.03%.

206. Allergan's failed research attempts also support non-obviousness. Allergan's scientists attempted several approaches which all resulted in failures. The goal of decreasing hyperemia while maintaining IOP lowering efficacy was not readily solvable. Many of these approaches were tested by scientists at Allergan other than the inventors in this case.

207. The Court finds that the inventors proceeded contrary to conventional wisdom in developing Lumigan® 0.01%. The prior art and wisdom taught that BAK should be reduced or eliminated from ophthalmic formulations. Moreover, there were no other reformulations that had ever increased the concentration of BAK, only examples of reducing or eliminating BAK. In fact, the conventional wisdom—demonstrated in the Higaki, Camber, and FDA Medical Review references—teaches that BAK would not enhance the penetration of bimatoprost, a small, neutral, lipophilic prostaglandin analog.

208. As discussed above, the Court finds that Allergan's research yielded unexpected results in increasing BAK concentrations with bimatoprost. Given the similar hyperemia rates of 0.03% and 0.01% bimatoprost shown in the Laibovitz reference, it was unexpected that Lumigan® 0.01% would be able to reduce the incidence and severity of hyperemia compared to treatment with Lumigan® 0.03% while also maintaining the IOP-lowering efficacy of Lumigan® 0.03%. It was also unexpected that 200 ppm BAK would enhance the penetration of bimatoprost into the eye, and specifically, that it would

increase permeation sufficiently to reduce bimatoprost concentration from 0.03% to 0.01% without any loss in efficacy and still meet regulatory standards.

209. Even after their initial research, the inventors and others at Allergan doubted the potential of a formulation using 0.01% bimatoprost and 200 ppm BAK.

210. The commercial success of Lumigan® 0.01% is proof of its innovation. Since its launch in October 2010, total prescriptions, market share, and gross sales have grown annually. For example, gross sales were $11,172,596 for the remainder of 2010, $138,643,391 for 2011, and $303,070,540 for 2012. Allergan expects gross sales for 2013 to top $500,000,000. It is currently Allergan's top-selling glaucoma product and the second best-selling drug in Allergan's entire eye care portfolio, Allergan's largest business unit. Defendants contend that the performance of Lumigan® 0.01% is due to its cannibalization of Lumigan® 0.03% sales, marketing efforts, and that the commercial success is more properly attributed to bimatoprost. The Court disagrees. Allergan's total Lumigan® business—which included both 0.03% and 0.01% products—expanded after the introduction of 0.01%, which was due to the unique features of Lumigan® 0.01%. The Lumigan® franchise continued to grow even after Lumigan® 0.03% was removed from the market in order to transition completely to Lumigan® 0.01%.

211. The strong commercial performance of Lumigan® 0.01% is particularly significant because in March 2011, a lower-priced, generic version of Xalatan® (with the active drug latanoprost)—which was then the best-selling prostaglandin—became available and quickly captured market share. Lumigan® 0.01% performed better than Allergan expected in light of the generic latanoprost launch, and Lumigan® 0.01% has since become the best-selling branded glaucoma drug in the United States. The fact that

consumers continued to purchase Lumigan® 0.01% despite having access to generic latanoprost demonstrates that Lumigan® 0.01% has unique attributes that fulfill a need unmet by any competitor.

212. The Court finds there is a nexus between the commercial success of Lumigan® 0.01%, which is an embodiment of the claimed invention.

J. Irreparable Harm

213. The Court finds that Allergan would be irreparably harmed if Defendants were permitted to enter the market with generic versions of Lumigan® 0.01%.

214. Allergan's market share would be quickly eroded with the introduction of generic products. Market erosion is expected when generics are introduced, as was the case with Xalatan®. While patented, Xalatan® was the leading drug in the prostaglandin-analog class, controlling approximately 50% of the prostaglandin market. When Xanatan® went off patent, generics flooded the market. Two months after the introduction of generics, Xalatan® lost 90% of its market share, and within 12 months it lost a total of 95% of its market share. Currently, branded Xalatan® maintains only 1% of the market. Lumigan® 0.01% would suffer the same fate if generics entered into the market.

215. In addition to lost market share, the price of Lumigan® 0.01% would also suffer erosion. Increased competition by cheaply available generics would put downward pressure on Allergan's price in order for Lumigan® 0.01% to remain competitive in the marketplace.

216. The Court also finds that the revenue loss from generic entry would directly affect Allergan's ability to invest in the development of new treatments, harming both Allergan and ailing patients.

217. It would be difficult, if not impossible, to quantify all these harms from lost sales, price erosion, lack of reinvestment potential, and injury to goodwill and reputation. This further demonstrates the harm is irreparable and could not be later compensated by an award of damages.

III. CONCLUSIONS OF LAW

A. Jurisdiction

1. The Court has jurisdiction over this case pursuant to 28 U.S.C. §§ 1331, 1338(a).
2. Pursuant to 35 U.S.C. § 271(e)(2)(a), the filing of an ANDA "provides an 'artificial' act of infringement that creates case-or-controversy jurisdiction to enable the resolution of an infringement dispute before the ANDA applicant has actually made or marketed the proposed product." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).
3. Venue is proper in the Eastern District of Texas under 28 U.S.C. § 1391(b).
4. Because this action arises under the patent laws, Federal Circuit precedent is controlling. *See* 28 U.S.C. § 1295(a)(1).

B. Burden of Proof

5. A patent holder asserting infringement bears the burden of proving its claim by a preponderance of the evidence. *See Siemens Med. Solutions USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279 (Fed. Cir. 2011).
6. A party challenging a patent's validity must overcome the presumption of validity and prove that claim by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011).

C. Infringement

7. "To prove infringement, a plaintiff must prove the presence of each and every claim element or its equivalent in the accused method or device." *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1378 (Fed. Cir. 2011).

8. Infringement is a two-step test. The first prong requires that "the claim must be properly construed to determine its scope and meaning." *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993). Next, "the claim as properly construed must be compared to the accused device or process." *Id.*

9. Because the filing of an ANDA application is an artificial act of infringement, the appropriate inquiry is whether the generic ANDA product would infringe the asserted patents if it was introduced into the market. *See Warner-Lambert*, 316 F.3d at 1365–66.

i. Direct Infringement

10. An entity is liable for direct infringement if it "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent." 35 U.S.C. § 271(a).

11. A patent holder must prove a claim for direct infringement by establishing that the accused product contains every limitation—either literally or under the doctrine of equivalents—of the asserted claim. *Star Scientific*, 655 F.3d at 1378.

12. Literal infringement requires that every claim limitation be present in the accused product. *Pozen Inc. v. PAR Pharm., Inc.*, 696 F.3d 1151, 1167 n.11 (Fed. Cir. 2012).

13. "Infringement under the doctrine of equivalents may be established by showing that 'the substitute element matches the function, way, and result of the claimed element.'" *Charles Mach. Works, Inc. v. Vermeer Mfg. Co.*, 723 F.3d 1376, 1380 (Fed. Cir. 2013) (quoting *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1356 (Fed. Cir. 2012)).

14. Infringement under the doctrine of equivalents frequently turns on questions of fact, such as "[w]hether the substitute element (1) has substantially the same function as the recited element, (2) achieves that function in substantially the same way, and (3) achieves substantially the same result." *Id.*

15. The Court finds that Allergan has proved by a preponderance of the evidence that Defendants' proposed ANDA products will directly infringe the asserted claims that cover the composition of Lumigan® 0.01%—i.e., claim 2 of the '504 Patent; claims 1, 7, and 8 of the '353 Patent; and claim 15 of the '479 Patent—if it makes, sells, offers to sell, or imports its proposed generic product in the United States.

16. Sandoz's proposed product includes 0.01% bimatoprost, 200 ppm BAK, citric acid monohydrate, a phosphate buffer, sodium chloride, and water, it has a pH of "about 7.3," it is formulated for ophthalmic administration, it is for the treatment of glaucoma or ocular hypertension, and it is to be used once-daily and applied topically (PTX-348; PTX-14C).

17. Sandoz's label and its representations to the FDA confirm that its product meets the clinical limitations of the asserted claims of the '353 and '118 Patents because it will have the same efficacy and hyperemia as Lumigan® 0.01%, which, as discussed previously, meets the claim limitations.

18. Therefore, the Court finds that Sandoz directly infringes claim 2 of the '504 Patent; claims 1, 7, and 8 of the '353 Patent; and claim 15 of the '479 Patent and that any patient or doctor using Sandoz's product would directly infringe claims 1, 7, and 8 of the '118 Patent and claims 1, 6, 10, and 12 of the '605 Patent.

19. Sandoz has stipulated that it infringes claim 2 of the ’504 Patent and claim 15 of the ’479 Patent, and that it meets many of the elements of the remaining asserted claims (Doc. No. 241 at 1–2).

20. Lupin’s proposed product includes 0.01% bimatoprost, 200 ppm BAK, citric acid monohydrate, a phosphate buffer, sodium chloride, and water, it has a pH of “about 7.3,” it is formulated for ophthalmic administration, it is for the treatment of glaucoma or ocular hypertension, and it is to be used once-daily and applied topically (PTX-13A; PTX-13B; PTX-13D).

21. Lupin’s label and its representations to FDA confirm that its product meets the clinical limitations of the asserted claims of the ’353 and ’118 Patents because it will have the same efficacy and hyperemia as Lumigan® 0.01%, which, as discussed previously, meets the claim limitations.

22. Therefore, the Court finds that Lupin directly infringes claim 2 of the ’504 Patent, claims 1, 7, and 8 of the ’353 Patent, and claim 15 of the ’479 Patent, and that any patient or doctor using Lupin’s product would directly infringe claims 1, 7, and 8 of the ’118 Patent and claims 1, 6, 10, and 12 of the ’605 Patent.

23. Watson’s proposed product includes 0.01% bimatoprost, 200 ppm BAK, citric acid monohydrate, a phosphate buffer, sodium chloride, and water, it has a pH of “about 7.3,” it is formulated for ophthalmic administration, it is for the treatment of glaucoma or ocular hypertension, and it is to be used once-daily and applied topically (PTX-15A; PTX-15D).

24. Watson’s representations to the FDA confirm that its product meets the clinical limitations of the asserted claims of the ’353 and ’118 Patents because it will have the

same efficacy and hyperemia as Lumigan® 0.01%, which, as discussed previously, meets the claim limitations.

25. Therefore, the Court finds that that Watson directly infringes claim 2 of the ’504 Patent; claims 1, 7, and 8 of the ’353 Patent; and claim 15 of the ’479 Patent and that any patient or doctor using Watson’s product would infringe claims 1, 7, and 8 of the ’118 Patent and claims 1, 6, 10, and 12 of the ’605 Patent.

26. Hi-Tech’s proposed generic includes 0.01% bimatoprost, 200 ppm BAK, citric acid monohydrate, a phosphate buffer, sodium chloride, and water, it has a pH of “about 7.3,” it is formulated for ophthalmic administration, it is for the treatment of glaucoma or ocular hypertension, and it is to be used once-daily and applied topically (PTX-12A; PTX-12B; PTX-12C).

27. Hi-Tech argues that its product does not meet the pH limitation of the claims. Hi-Tech disclosed in its ANDA that the pH range for its product during its shelf life is 6.8–7.2. The asserted claims of the ’502, ’497, and ’605 Patents all require a pH of “about 7.3” (*See* PTX-1 at 6:21). The Court finds that the pH range for Hi-Tech’s generic literally infringes, and in the alternative, infringes the claims under the doctrine of equivalents. During claim construction, the Court adopted the parties’ agreed construction of the phrase “about 7.3”: “approximately 7.3” (Doc. No. 118 at 16). Hi-Tech’s range includes an upper limit of 7.2. The Court finds that a pH of 7.2 literally meets the requirement of “approximately 7.3.” The Court also finds that a pH range of 6.8–7.2 literally meets the “about 7.3” claim limitation.

28. The Court also finds that the pH range of Hi-Tech’s product of 6.8–7.2 meets the claim limitation of “about 7.3” under the doctrine of equivalents. From a chemical standpoint,

the Court finds no appreciable difference in a pH from 6.8–7.2 and a pH of "about 7.3." The Court finds that a pH in Hi-Tech's proposed range performs substantially the same function as a pH of "about 7.3" (ensuring the formulation is stable and comfortable for ophthalmic administration), achieves that function in the same way (by keeping the pH of the formulation relatively close to the pH of the tear film and at a level where the active ingredient is stable), and achieves substantially the same result (a stable formulation that delivers the active ingredient to the patient's eye so that it can be absorbed). This is consistent with Hi-Tech's representation to the FDA that its proposed product is bioequivalent to Lumigan® 0.01%.

29. The Court also finds that Hi-Tech's prosecution history estoppel argument regarding pH is without merit.

30. "Where an amendment narrows the scope of the claims, and that amendment is adopted for a substantial reason related to patentability, the amendment gives rise to a presumption of surrender for all equivalents that reside in 'the territory between the original claim and the amended claim.'" *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1291 (Fed. Cir. 2010) (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 740 (2002)).

31. "This presumption can be overcome by showing that 'at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent.'" *Id.* (quoting *Festo*, 535 U.S. at 741).

32. "One way to make this showing is to demonstrate that 'the rationale underlying the narrowing amendment bore no more than a tangential relation to the equivalent in

question.'" *Id.* (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1368 (Fed. Cir. 2003) (en banc)).

33. "Although there is no hard-and-fast test for what is and what is not a tangential relation, it is clear that an amendment made to avoid prior art that contains the equivalent in question is not tangential." *Id.*

34. The Court concludes that the amendments during prosecution were all tangential to the pH issue. The amendments dealt with eliminating independent claims with broad ranges of concentrations for bimatoprost and BAK. These claims included no pH limitations. The narrower dependent claims contained specific requirements for bimatoprost, BAK, and pH. Therefore, the Court finds that the amendments that added the pH limitation were tangential to the amendments regarding bimatoprost and BAK concentration range. At the same time Allergan amended the asserted claims, it also added new claims to a method of using 0.01% bimatoprost with 200 ppm BAK but without any pH limitation. Although the PTO examiner rejected these claims as procedurally improper (i.e., inserting new claims in a Request for Continued Examination), it highlights that Allergan did not intend to surrender any subject matter regarding pH. Accordingly, the Court finds that prosecution history estoppel does not preclude use of the doctrine of equivalents in this case.

35. For the above reasons, the Court finds that Hi-Tech directly infringes claim 2 of the '504 Patent and claim 15 of the '479 Patent, and that any patient or doctor using Hi-Tech's product would infringe claims 1, 6, 10, and 12 of the '605 Patent.

36. The Court also finds that Hi-Tech infringes claims 1, 7, and 8 of the ’353 Patent and claims 1, 7, and 8 of the ’118 Patent. None of these asserted claims include a specific limitation regarding pH, thus all of Hi-Tech’s pH arguments are inconsequential.

37. Hi-Tech additionally contends that the ’353 and ’118 Patents are unenforceable under the equitable defense of prosecution laches.

38. “The doctrine ‘may render a patent unenforceable when it has issued only after an unreasonable and unexplained delay in prosecution’ that constitutes an egregious misuse of the statutory patent system under the totality of the circumstances.” *Cancer Research Tech. Ltd. v. Barr Labs., Inc.*, 625 F.3d 724, 728 (Fed. Cir. 2010) (quoting *Symbols Techs., Inc. v. Lemelson Med., Educ., & Research Found.*, 422 F.3d 1378, 1385 (Fed. Cir. 2005)). “To establish prejudice an accused infringer must show evidence of intervening rights, *i.e.*, that either the accused infringer or others invested in, worked on, or used the claimed technology during the period of delay.” *Id.* at 729.

39. The Court does not find any delay by Allergan unreasonable. Allergan filed the initial patent application that led to the asserted patents on March 16, 2005. That application included broad independent claims without the pH limitation and narrower dependent claims with a pH limitation of 7.4. The claims without the pH limitation remained pending until they were cancelled on August 18, 2010. On February 10, 2012, Allergan filed continuation applications that led to the ’353 and ’118 Patents, this application—and the resulting patents—included claims without pH limitations. From August 18, 2010, until February 10, 2012, all of Allergan’s pending claims included a pH limitation. Hi-Tech argues that the period of delay spans from March 2005, until February 2012. Allergan maintains that the only period of delay is between August 2010, and February

2012, the period during which Allergan did not have pending claims without the pH limitations. The Court agrees with Allergan. Between August 2010 and February 2012, is the only time when Hi-Tech could argue that it could have designed around Allergan's patents with respect to the pH limitation. The Court does not find this 18 month delay unreasonable. Even under Hi-Tech's calculated delay, the Court does not find that Allergan unreasonably delayed under the totality of the circumstances. *See Holmes Grp. v. RPS Prods., Inc.*, No. 03-40146-FDS, 2010 WL 7867756, at *9 (D. Mass. June 25, 2010) (finding that a delay of "only five to seven years" did not amount to unreasonableness). Moreover, the Court does not find that Allergan engaged in an egregious misuse of the patent system in prosecuting its claims. In summary, the Court does not find that Hi-Tech's equitable defense of prosecution laches is meritorious.

40. Accordingly, the Court finds that Hi-Tech directly infringes claims 1, 7, and 8 of the '353 Patent, and that patients and doctors using Hi-Tech's product would directly infringe claims 1, 7, and 8 of the '118 Patent.

ii. Indirect Infringement

41. An entity is liable for indirect infringement if it induces or contributes to infringement.

42. The Court finds that Allergan has proved by a preponderance of the evidence that each Defendant will induce or contribute to the infringement of the asserted claims that cover methods of using Lumigan® 0.01%—i.e., claims 1, 7, and 8 of the '118 Patent and claims 1, 6, 10, and 12 of the '605 Patent—if it makes, sells, offers to sell, or imports its generic product in the United States. *See* 35 U.S.C. §§ 271(b)–(c).

a. Induced Infringement

43. A party is liable for induced infringement if it "actively induces infringement of the patent." 35 U.S.C. § 271(b).

44. "In order to prevail on an inducement claim, the patentee must establish 'first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement.'" *ACCO Brands, Inc. v. ABA Locks Mfr. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007) (quoting *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1304–05 (Fed. Cir. 2002)).

45. In other words, "[a] finding of inducement requires both knowledge of the existence of the patent and 'knowledge that the induced acts constitute patent infringement.'" *Commil USA, LLC v. Cisco Sys., Inc.*, 720 F.3d 1361, 1367 (Fed. Cir. 2013) (quoting *Global-Tech Appliance, Inc. v. SEB S.A.*, 131 S.Ct. 2060, 2068 (2011)).

46. The intent element also is satisfied where an infringer was willfully blind to any infringement. *Global-Tech Appliances*, 131 S. Ct. at 2068–69.

47. "[A] willfully blind defendant is one who takes deliberate actions to avoid confirming a high probability of wrongdoing and who can almost be said to have actually know the critical facts." *Id.* at 2070–71.

48. "Accordingly, inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc).

49. Intent can be proven by either direct or circumstantial evidence. *See Fuji Photo Film Co. v. Jazz Photo Corp.*, 394 F.3d 1368, 1377 (Fed. Cir. 2005).

50. Importantly, "[i]ntent is a factual determination particularly within the province of the trier of fact." *Allen Organ Co. v. Kimball Int'l, Inc.*, 839 F.2d 1556, 1567 (Fed. Cir. 1988).

51. In this case, Defendants knew of the asserted patents at least as of the filing of the complaints in these consolidated cases. As addressed previously, direct infringement would occur by instructing doctors and patients with the proscribing information of a generic 0.01% bimatoprost product to use it in an infringing manner, that is for treating glaucoma or ocular hypertension. Defendants would possess the specific intent to cause that infringement.

52. Defendants' proposed prescribing information and labeling is also proof that there is no non-infringing use for any of the Defendants' products and further establishes Defendants' specific intent to infringe. *See AstraZenca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) ("In the context of specific intent, it is irrelevant that some users may ignore the warnings in the proposed label. The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the accused infringer's] affirmative intent to induce infringement.").

53. The Court finds that Defendants are liable for induced infringement of claims 1, 7, and 8 of the '118 Patent and claims 1, 6, 10, and 12 of the '605 Patent.

b. Contributory Infringement

54. "Contributory infringement occurs if a party sells or offers to sell, a material or apparatus for use in practicing a patented process, and that 'material or apparatus' is material to practicing the invention, has no substantial non-infringing uses, and is known by the party 'to be especially made or especially adapted for use in an infringement of such patent.'" *In re Bill of Lading Transmission & Processing Sys. Patent Litig.*, 681 F.3d 1323, 1337 (Fed. Cir. 2002) (quoting 35 U.S.C. § 271(c)).

55. Defendants knew of the asserted patents at least as of the filing of the complaints in these consolidated cases. If Defendants' products are approved by the FDA, Defendants will each sell a product that patients and doctors will use to infringe. Defendants' products meet all the limitations of the asserted claims, and use of Defendants' generics would infringe all the asserted claims. Defendants' products are a material part of the invention, specifically, the method claims cover a method of administering the product to treat glaucoma or ocular hypertension.

56. Finally, there are no non-infringing uses for any of Defendants' products. Rather, the proposed labeling instructs patients to use the product in an infringing manner.

57. Therefore, the Court finds that Defendants are all liable for contributory infringement of claims 1, 7, and 8 of the '118 Patent and claims 1, 6, 10, and 12 of the '605 Patent.

D. Invalidity

i. Obviousness

58. A patent is invalid "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103

59. Obviousness is a legal finding underpinned by factual findings. *See In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009).

60. "An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any." *Id.*

61. "The teachings of a prior art reference are underlying factual questions in the obviousness inquiry." *Id.*

62. "A party seeking to invalidate a patent based on obviousness must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (internal quotations omitted). While the patent owner has the burden of going forward with rebuttal evidence if the challenger successfully presents a prima facie invalidity case, this "does not in substance shift the burden of persuasion, because the presumption of validity remains intact and *the ultimate burden of proving invalidity remains with the challenger throughout the litigation.*" Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd., 719 F.3d 1346, 1352 (Fed. Cir. 2013) (emphasis original).

63. The patentee can meet its burden of production with evidence of objective indicia of non-obviousness. These include "(1) commercial success; (2) long felt need; (3) copying; (4) unexpected results; (5) acceptance by others; and (6) initial skepticism." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1370 (Fed. Cir. 2012); *see also Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1352 (Fed. Cir. 2010) (explaining that praise from a competitor in the industry related to the patented features is evidence of non-obviousness).

64. In order to prevent hindsight bias, "the proper analysis requires a form of amnesia that 'forgets' the invention and analyzes the prior art and understanding of the problem at the date of invention." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012).

65. In light of the facts previously outlined, the Court finds that ophthalmic formulation is an unpredictable art. Results in this field are generally more likely to be unexpected. *See Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)). Yet while "formulation science carries with it a degree of unpredictability, 'obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.'" *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). But here, not only did the prior art not suggest that there were a finite number of predictable solutions, the Burstein reference taught that using 200 ppm BAK in humans would not increase permeability in humans.

66. "Evidence of obviousness, especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012) (internal quotations omitted). "[W]here the prior art, at best, '[gives] only general guidance as to the particular form of the claimed invention or how to achieve it,' relying on an 'obvious-to-try' theory to support an

obviousness finding is 'impermissible.'" *Id.* (quoting *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)).

67. In light of the Court's factual findings, Defendants have failed to prove by clear and convincing evidence that any asserted claim would have been obvious to a person of ordinary skill in the art at the time of the invention. The most important considerations include: (1) that there were significant differences between the prior art and the asserted claims; (2) that there was no reason to select the claimed concentrations of bimatoprost and BAK in the range disclosed in the prior art; (3) that a person of ordinary skill in the art would have had no reasonable expectation that combining the prior art to arrive at the claimed invention would lead to success; (4) that the prior art taught away from the claimed invention; and (5) that the objective indicia all strongly demonstrate non-obviousness.

68. The Court also rejects Defendants' arguments that the asserted claims would have been obvious under an "obvious to try" theory. The Court finds that the field of ophthalmic formulation is unpredictable because: (1) there were many possible solutions to the formulation problem; (2) the field was unpredictable; (3) there was skepticism in the field regarding the use of BAK; and (4) the prior art taught away from the claimed invention. The Court finds that a person of ordinary skill in the art would not have had a reasonable probability of success in developing the invention. The Court also finds that it would not have been obvious to try the claimed invention. The prior art taught away from the claimed invention by teaching: (1) that bimatoprost lost efficacy as its concentration decreased; (2) that BAK had no impact on bimatoprost's permeability; and (3) that BAK

was cytotoxic and could cause corneal disorders, therefore encouraging the elimination or reduction in the concentration of BAK.

69. Finally, the Court rejects Defendants' arguments that *Galderma Labs., L.P. v Tolmar, Inc.*, 737 F.3d 731, (Fed. Cir. Dec. 11, 2013), compels this Court to find the asserted claims obvious. First, Defendants failed to presented a prima facie case of invalidity by demonstrating that (1) "there is a range disclosed in the prior art" for both bimatoprost and BAK; (2) "the claimed invention falls within that range"; and (3) "there was motivation to select the claimed [concentration of the] composition in the disclosed range." *See id.* at 737–38. And, even assuming that Defendants presented its prima facie case, Allergan has met its burden of producing rebuttal evidence, i.e., "that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Id.* at 738.

70. As Defendants note, the Orange Book patent for the predecessor Lumigan® 0.03% product discloses a range of bimatoprost concentrations ("preferably about 0.001 to about 1.0%") and concentrations of BAK (0–0.10% or to 1000 ppm) (*see* Doc. No. 301-1 at 3–4). Other prior art references also disclose similar ranges. The claimed invention falls within those ranges. And, by Allergan's own admission, there was a motivation to select a lower concentration of bimatoprost because it was known in the prior art that bimatoprost causes hyperemia. But Defendants have failed to produce any evidence as to why one of ordinary skill in the art would select a BAK concentration of 200 ppm given that the prior art was explicitly disparaging of BAK. In fact, Defendants' expert witness, Dr. Samples, had serious concerns about BAK since 1983 and used facetious

hyperboles—such as stating that "BAK is from Satan" or calling BAK "a natural-born killer"—to draw the ophthalmic community's attention to BAK's cytotoxicity (*see* Trial Tr., Doc. No. 251 at 60:11–61:15; 86:20–88:24). Thus, one of ordinary skill in the art at the time of the invention would have been motivated to reduce or eliminate BAK—not increase its concentration—from ophthalmic solutions, and Defendants failed to provide any evidence to the contrary.

71. Furthermore, assuming, *arguendo*, that Defendants established its prima facie case of obviousness, Allergan has produced ample rebuttal evidence. First, as noted above, prior art taught away from choosing a high concentration of BAK. Second, maintaining the same efficacy while decreasing the bimatoprost is an unexpected result of a different *kind*, not just of different *degree*. As noted above, both Laibovitz and Lyons taught that decreasing the bimatoprost concentration results in lower efficacy. The patentees were able to reach the opposite result (by using 200 ppm BAK). This is clearly distinguishable from *Galderma*, where "an unexpected increase in efficacy is measured by a small percentage[.]" *See* 737 F.3d at 739. Here, the patentees were able to *reverse* the concentration–efficacy relationship known in the prior art by choosing a higher concentration of BAK. And it was not known in the prior art nor was it inherent that increased concentrations of BAK would lead to a significant increase in bimatoprost penetration. *See Allergan*, 726 F.3d at 1294. Finally, other secondary considerations—such as commercial success, long felt need, failure of others, and initial skepticism—all point in Allergan's favor. The commercial success here, unlike *Galderma*, is demonstrated by its status as the best-selling branded glaucoma drug in the United States despite the generic latanoprost launch in March 2011. For years since Lumigan® 0.03%'s

launch in 2002, researchers experienced much trial and error to reduce the hyperemia side effect. Even after deciding to further study the formulations with 200 ppm BAK, Allergan's own researchers were initially skeptical of formulation of the claimed invention (with 0.01% bimatoprost) because those concentrations were chosen to be tested as a control group and not as a viable solution. Their skepticism is further evidenced by the fact that they continued to pursue formulations without BAK (e.g., calcium borate, cyclodextrin, and EDTA). In sum, the Court finds that all of the objective indicators weigh strongly in favor of nonobviousness.

72. Based upon the totality of the evidence, the Court finds that Defendants have not proved by clear and convincing evidence obviousness of claim 2 of the '504 Patent; claim 15 of the '479 Patent; claims 1, 7, and 8 of the '353 Patent; claims 1, 7, and 8 of the '118 Patent; or claims 1, 6, 10, and 12 of the '605 Patent.

ii. Written Description Requirement

73. In addition to obviousness, Defendants contend that Allergan's patents directed to the use of the invention to treat glaucoma and ocular hypertension in humans do not meet the written description requirement of 35 U.S.C. § 112. Defendants argue that the patents are invalid because the written description does not also include human clinical data. Specifically, Defendants challenge the written description for claims 1, 7, and 8 of the '353 and '118 Patents.

74. Defendants did not present any evidence or argument on this issue at trial.

75. The written description requirement under 25 U.S.C. § 112 requires that a patent "must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989); *see also Ariad Pharm., Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

76. Therefore, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351.

77. "[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id*.

78. The Court finds that disputed claims have adequate support in the written description.

79. The formulation for Lumigan® 0.01% is explicitly disclosed in the specification and is identified as the best mode of the invention. Lumigan® 0.01% has the clinical performance that is recited in the claims—i.e., nearly equivalent efficacy and less hyperemia than Lumigan® 0.03%.

80. The patents in suit are all entitled "Enhanced Bimatoprost Ophthalmic Solution," and they present *in vivo* and *in vitro* rabbit data comparing the permeability and ocular absorption of bimatoprost in various test formulations as compared to Lumigan® 0.03%. The specification also includes an example in which "intraocular pressure drops more and less hyperemia is observed" from administration of a formulation with 0.015% bimatoprost, 125 ppm BAK, and 0.015% EDTA than of Lumigan® 0.03% (PTX-3 at 40–45). A person of ordinary skill in the art would conclude—upon reading these disclosures—that the specification adequately describes the clinical performance requirements in the asserted claims, especially given the express disclosure that Lumigan® 0.01% is an example of the best mode of the invention.

81. The specification here satisfies the written description requirements because it discloses the exact formulation for Lumigan® 0.01% and the animal testing data that led the

inventors to take the 0.01% bimatoprost and 200 ppm BAK formulation that became Lumigan® 0.01% into Phase II human testing.

82. Additionally, the Court finds that the inventors had possession of the invention before they filed the original patent in March 2005 based on the contemporaneous documents. For example, the clinical protocol that described the procedures for the initial human clinical studies on Lumigan® 0.01% explained that the "clinical hypotheses" were that "[a]t least one investigational test formulation has less hyperemia when compared to LUMIGAN® [0.03%] once-daily" and that "[a]ll investigational test formulations are comparable to LUMIGAN® [0.03%] once-daily in intraocular pressure lowering effects" (PTX-48B at 13–14). The Clinical Protocol Review Committee at Allergan signed off on the protocol by November 17, 2004, and then submitted it to the FDA for approval. The Phase II human clinical studies based on the protocol began in January 2005. All of this occurred before the March 2005 filing date of the original patent. This establishes that the inventors had possession of the invention before they filed the original patent application.

83. Accordingly, the Court finds that Defendants have failed to prove by clear and convincing evidence the asserted claims of the '353 and '118 Patents are invalid for lack of written description.

iii. Enablement Requirement

84. Lupin additionally alleges that the asserted patents are not sufficiently enabled because they do not include the results of human clinical studies.

85. Lupin did not present any evidence or argument on this issue at trial.

86. Enablement under 35 U.S.C. § 112 requires that "the specification must enable one of ordinary skill in the art to practice the claimed invention without undue experimentation." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed.

Cir. 1999); *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1355 (Fed. Cir. 2012).

87. Several factors that may assist the Court in determining whether experimentation is undue are:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

88. "Although the ultimate determination of whether one skilled in the art could make and use the claimed invention without undue experimentation is a legal one, it is based on underlying findings of fact." *Warner-Lambert Co. v. Teva Pharm. USA, Inc.*, 418 F.3d 1326, 1337 (Fed. Cir. 2005).

89. The Manual of Patent Examining Procedures (MPEP) used by PTO examiners during prosecution "instructs examiners to give presumptive weight to the utility for which human trials have been initiated." *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 924 (Fed. Cir. 2011). "Before a drug can *enter* human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those *especially* skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful." *Id*. (quoting MPEP § 2107.03).

90. Based upon the entirety of the evidence, the Court finds the claims are adequately enabled. *See id.* at 925–26. As corroborated by Allergan's contemporaneous research at the time of filing, Lumigan® 0.01% has the clinical performance as recited in the asserted claims and is disclosed as the best mode in the specification. Thus,

specification's disclosure of the Lumigan® 0.01% formulation would enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation.

E. Injunctive Relief

91. Under the Hatch-Waxman Act, "the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." 35 U.S.C. § 271(e)(4)(A).

92. The Hatch-Waxman Act also provides that "injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product." 35 U.S.C. § 271(e)(4)(B).

93. A permanent injunction is appropriate when a party demonstrates: "(1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006).

i. Irreparable Harm and Inadequate Remedies at Law

94. As previously addressed, Allergan would suffer irreparable harm if Defendants are not enjoined. Allergan would lose significant revenue, irreversibly lose market share, suffer price erosion, have an inability to reinvest in future research, and suffer damage to its goodwill and market reputation.

95. "Irreparable injury encompasses different types of losses that are often difficult to quantify, including lost sales and erosion in reputation and brand distinction." *Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336, 1344 (Fed. Cir. 2013).

96. The entry into the market by Defendants' generics would irreparably harm Allergan. Those injuries are difficult to quantify. *See id.* Remedies at law, such as monetary damages, would not adequately compensate Allergan for its injury.

ii. Balance of Equities

97. The Court finds that the balance of equities favors Allergan.

98. Upon entry of Defendants' ANDA products into the market, Allergan will suffer irreparable harm. The Court does not find that Defendants would suffer little to no harm from continuing to be excluded from the market until the expiration of the patents in suit.

iii. Public Interest in an Injunction

99. The Court finds that the public interest is best served by the issuance of an injunction.

100. A fundamental premise of the patent system is encouraging innovation. "The encouragement of investment-based risk is the fundamental purpose of the patent grant, and is based directly on the right to exclude." *Patlex Corp. v. Mossinghoff*, 758 F.2d 594, 599 (Fed. Cir. 1985).

101. Although Defendants' generic products would increase competition and make the drug available at lower prices, the Court does not find this outweighs the importance of patent protection. *See Douglas Dynamics*, 717 F.3d at 1346 ("[T]he public has a greater interest in acquiring new technology through the protections provided by the Patent Act than it has in buying 'cheaper knock-offs.'").

102. Accordingly, the Court grants Allergan's request for a permanent injunction. Defendants shall be enjoined from making, using, importing, selling, or offering to sell

their ANDA products in the United States, or inducing others to manufacture, use, import, offer to sell, or sell their ANDA products in the United States until the expiration of Allergan's asserted patents.

IV. CONCLUSION

103. Based upon the evidence, the Court finds that Allergan has proven by a preponderance of the evidence that Defendants infringe all asserted claims of Allergan's patents.

104. The Court finds that Defendants have failed to rebut the presumption of validity of Allergan's patents by clear and convincing evidence. Therefore, the Court does not find that Allergan's patents are invalid or unenforceable.

105. In accordance with 35 U.S.C. § 271(e)(4)(A), the Court orders that the effective date of FDA approval of any of the drugs described in Defendants' ANDAs 203056, 202911, 203748, and 203604, will be a date that is not earlier than the date of the expiration of all of U.S. Patent Nos. 7,851,504; 8,278,353; 8,299,118; 8,309,605; and 8,338,479.

106. The Court grants Allergan's request for a permanent injunction as addressed in the Court's contemporaneously filed Final Judgment and Permanent Injunction.

It is SO ORDERED.

SIGNED this 13th day of January, 2014.

MICHAEL H. SCHNEIDER
UNITED STATES DISTRICT JUDGE